SOMATOSENSORY EVOKED POTENTIALS (SEP) IN RELATION TO NOCICEPTION AND ANESTHESIA

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CONTENTS

Pain is an unpleasant sensation, and it is the most common symptom of which man and animals want to be relieved.

Its physiological substratum is stimulation of the peripheral nervous system and conduction to the central nervous system.

Basically, pain is a subjective experience in human beings, so it is not surprising that the description of pain is difficult to interpret.

Animals cannot express pain sensations verbally as human beings can. When the functions of pain, one of nature's earliest signs of morbidity, are considered, one may ask the question: do animals experience pain consciously? DUMAS (1937) stresses the importance of this point in man: 'Le sourire spontane est la réaction de la plus facile des muscles du visage pour une excitation modérée'.

Nowadays it is generally agreed that animals do experience pain consciously. One can recognise the reaction to noxious stimuli and notice signs of stress among the animals. The anatomical and physiological patterns for the conduction of various messages are very similar in man and animals (BIEDENBACH 1979).

Behavioral studies have shown that animals experience pain consciously; they are capable of associating noxious stimuli with other stimuli (PAVLOV 1960). From psychological studies we know that operant conditioning and rewarding stimuli are the best ways to teach animals new tasks and are specially suitable for the study of pleasurable situations.

Recording and measuring pain intensity in animals is very difficult. For human subjects it has been shown experimentally that there are no significant differences in threshold levels for pain in different cultures; nevertheless, people do react in a variety of ways to pain. Pain in man and animals is influenced by secondary factors. In animals, as in man, the threshold levels for pain are the same (VIERCK 1976). The peripheral substratum for pain in the somatosensory system is thus the same throughout the animal kingdom.

Moreover the motor response following a painful stimulus is not uniform: we do not even know whether this response is a reflex or a conscious behavior.

The purpose of this study was to seek an answer to the following questions: does registration of somatosensory evoked potentials (SEP) give an indication of the degree to which painful stimuli reach the central regions of the brain and does it thus provide a 'scale' of the degree to which these stimuli are felt as 'pain', so that the efficacy of anesthesia or analgesia can be 'measured' from the decrease in intensity or latent periods of these potentials.

For the work described in this thesis we have used a method which has been used before, but in ou experiments it has been extended in order to register the electrophysiological responses in different brain regions after noxious stimulation. We assume that if no cortical responses are observed after painful stimulation no pain is felt.

We first investigated which responses are important in pain perception and to what extent these responses are reduced by anesthetics.

In human subjects these responses can be compared with the verbal reaction to pain which can be used as an extra, though more subjective, form of information.

CHAPTER 1

PAIN AND ITS RECOGNITION

1.1. Introduction

Of all sensory modalities pain has for centuries attracted the most attention from physicians, philosophers, scientists and physiologists.

ARISTOTLE equated pain with unpleasantness whether arising from outside the body, within the body or within the 'soul' (as when one feels miserable). 'Pain or unpleasantness' stood for him as the opposite to 'pleasure' and he considered every action to be 'accompanied by pleasure or pain'.

Our word 'pain' is derived from the latin word 'Poena' which means 'punishment'. For SPINOZA pain was a focal form of sorrow which he called one of the three primary emotions. Pain, which he thought of as the emotion opposite to 'pleasurable excitement', he related to 'a man when one of his parts is affected more than the others'.

As the 20th century began, pain was widely accepted as a sensory experience rather than the emotional reaction opposite to pleasure.

VON FREY (1896) even proposed a specific receptive and transmission system for various modalities of cutaneous sense, including pain.

A few years later SHERRINGTON (1906) emphasized that no specific transmission system for pain is present but that pain usually results from the threat of tissue destruction. He was the first to use the terms noxious and nociception. Every sense organ is capable of nociception if the intensity of stimulus exceeds a certain threshold, the pain threshold. Both theories seem to be true, as will be discussed in the next paragraph.

As scientists now tend to use it the word 'pain' conveys the above mentioned Spinozostic implication that the unpleasant feeling is specifically referred to some place or places in the body and that the function of pain both in humans and animals is a signal, not only of danger from the outside, but also of destructive processes from the inside.

If we are correct in believing that the common denominator for painful stimuli in ordinary or 'normal' circumstances is their noxious quality, then man and animals must have means for distinguishing noxious from innocuous environmental events.

Pain is a bifactorial phenomenon, comprising on the one hand a physiological response to nociceptive stimulation of certain nervous pathways and on the other hand the central appreciation of these physiological events, which will in turn produce specific changes in the behavior of the individual.

With the operation of frontal leucotomy in man it was discovered that the sensations of pain and the accompanying unpleasant emotions could be separated by neurosurgery. The subjects would feel pain when a noxious stimulus was applied but they no longer suffered from the unpleasant sensations of pain (NATHAN 1977).

The experience of pain is an immensely complex physiological phenomenon. Until the 19th century it was believed that animals are not capable of feeling pain. Nowadays it is generally accepted that animals can also have unpleasant sensations accompanying pain, since nociceptive stimuli are used by almost everyone to influence the conduct of an animal. It is however, extremely difficult to diagnose or measure pain in animals (YOXALL 1978).

Acute transient pain, such as that produced by pricking the skin with a noxious agent such as a needle can readily be identified by the signs of distress elicited from the animal.

In other cases the presence of pain is demonstrated by behavioral changes, for example avoidance of traction upon surgical wounds or a high muscle tension in peritonitis.

Sometimes the presence of pain, especially prolonged pain, may be inferred from definite clinical signs such as lameness, dysphagia, weight loss, dysuria etc.

Whether a stimulus is painful for animals is hard to determine. The possibility of tissue destruction and one's own experience of pain in different circumstances are useful guides. In this context it is also worth bearing in mind that the threshold of pain perception appears to be remarkably constant across the species (VIERCK 1976). The tolerance - the maximal intensity of pain which is tolerated - may vary between individuals and also according to circumstances. Conventionally, stimuli and messages are called 'noxious' instead of 'painful' when animals are concerned. Nociception is the delivery to the brain of noxious messages. In pain the unpleasant sensation also plays an important role.

Measuring pain in animals is extremely difficult. The verbal reports which give us information about the emotional state of a human being cannot be used in animals. From the behavior and learned conduct of animals we have to deduce that an animal is capable of perceiving noxious stimuli and can suffer from discomfort or distress sensations. But also from analogies between man and animals, such as the architecture of the nervous system and the existence of a uniform pain threshold, it can be concluded that noxious stimulation is also unpleasant for animals.

In this chapter a brief review of the neurophysiological basis of nociception, a review of the methods of pain measurement and an outline of the study described in this thesis are presented.

1.2. Neurophysiological basis of nociception

From many tissues and organs noxious stimuli can be transmitted to the cortex. Via a large number of neurons and synapses the noxious impulses enter the brain. The many synapses especially can strongly modulate the impulse. The architecture of the nociceptive pathways is the same in all mammals. For a better understanding of the somatosensory evoked potential, knowledge about this part of the nervous system is necessary.

Pain receptors and peripheral nerves

Special receptors are necessary for transformation of physical and chemical stimuli into nerve action potentials. In the skin and muscle highly specialized tactile bodies, for example Pacinian corpuscles and muscle spindles, are present. Besides these specialized bodies, lancet free nerve endings are also present, sometimes even extending into epithelial structures.

Immediately after painful stimulation of the skin there is a local strong vasodilatation followed by edema. In the vicinity a less intense vasodilatation is seen. The pain threshold in this area is lowered (ROLLY and BILSBACK 1981).

For transport of the impulse to the spinal cord the peripheral nerves are important. In these peripheral nerves different types of fibers exist. They are divided into $A\alpha$, $A\beta$, $A\delta$, $A\gamma$, B and C fibers. $A\alpha$ fibers have a fast conduction velocity and the thickest myelin sheath and the C fibers have the lowest conduction velocity and are not myelinated

(ERLANGER and GASSER 1937).

The conduction velocities were investigated by recording action potentials of single fibers. By the use of this technique, combined with modifications in stimulus modality (beat and pressure) and stimulus strength (nonnoxious and noxious), fibers could be divided into specialized receptors sensitive to one modality and nonspecialized polymodal receptors sensitive to different kinds of stimuli. Some of these fibers respond to both innocuous and noxious stimuli (low threshold nociceptors) (PERL 1971), while others specifically respond only to noxious stimuli (high threshold nociceptors) (IGGO 1960).

Nociceptors are found in the Aδ, and C fiber groups. Aδ and C fibers are activated by needle pricks, pressure of 5-6 gram, pinching the skin, prolonged heat and chemical agents such as histamine, papain subepidermally and stinging nettles (VAN HEES and GYBELS 1972). TOREBJÖRK and HALLIN (1973) discovered that when only myelinated Aδ fibers were conducting an intense electrical stimulus was 'perceived' as a short sometimes sharp 'blow' i.e. sensations of localized pricking pain. When only nonmyelinated polymodal C fiber nociceptors are activated they go on firing for many seconds and even for minutes and evoke sensations of burning pain (DYKES 1975). It must be added that Aδ and C fibers are not exclusively for pain perception but that some of them also respond to nonnoxious stimuli.

The afferent nociceptive fibers, which have their cell bodies in the dorsal ganglion, enter the spinal cord via the dorsal roots and terminate in the dorsal horn of the spinal cord. The dorsal horn of the spinal cord was shown to be composed of different laminae by REXED (1954) on the basis of histology. In primates lamina I is concerned particularly though not exclusively with nociception (PERL 1971, CHRISTENSEN and PERL 1970). Neurons of this lamina send their axons via the neospinothalamic tract (only present in primates) to the thalamus. There is only one synapse between the peripheral nerve and this neospinothalamic tract.

Noxious stimuli activate besides the cells in lamina I, also parts of laminae IV, VI, VII and VIII (TREVINO et al. 1972, TREVINO et al. 1973, LEVANTE and ALBE-FESSARD 1972) in both primates and lower mammals.

There are also large numbers of cells in lamina V which respond to both myelinated and unmyelinated nociceptive afferents (WALL 1967).

Many of the fibers in the dorsal roots have their central endings subjected to presynaptic inhibition. The substantia gelatinosa, composed of lamina II and III, plays an important role in this presynaptic inhibition. Presynaptic inhibition is mediated through axoaxonal synapses. An excitant neuron induces a depolarisation of the presynaptic nerve ending and an inhibition of the release of transmitter in the synapse (BERNARDS 1980). The existence of presynaptic inhibition was first suggested by MENDELL and WALL (1964), and was the basis of the 'gate control' theory of MELZACK and WALL (1965). The substantia gelatinosa is activated by fast conducting fibers (Aβ) and deactivated by Aδ and C fibers; the activated substantia gelatinosa inhibits through presynaptic inhibition the conduction of nociceptive impulses to the brain. The existence of this presynaptic inhibition is in doubt, as WALL (1978) stated in a re-examination and restatement of the gate control theory of pain mechanisms: 'All the cells so far discovered which transmit information from nociceptors are inhibited by low threshold afferents and by descending controls. The mechanism by which this control is achieved remains completely unknown. Presynaptic inhibition as a phenomenon isolated from postsynaptic inhibition is in doubt. Whether the inhibition and facilitation are presynaptic or postsynaptic or both is unknown. That the gate control exists is no longer open to doubt but its functional role and its detailed mechanism remain open for speculation and for experiment'.

Postsynaptic inhibition is mediated through a transmitter released at the end of the axon which inhibits depolarisation of the postsynaptic membrane. Considerable modulation of the nociceptive impulse already occurs in the spinal cord, also by descending tracts, as will be discussed later.

Lissauers' tract also plays a prominent role in relaying these excitatory and inhibitory effects to adjacent spinal regions, by providing a strong (and probably modulatory) second input to the substantia gelatinosa at those more distant points (NATHAN 1977).

For the orofacial region the trigeminal nucleus caudalis in the medulla oblongata is the primary station for nociception. In the trigeminal nerve there are also types of small myelinated and unmyelinated afferents that respond exclusively or maximally to noxious stimuli.

The neurons in this nucleus caudalis are subjected to considerable

modulation from more rostral brain centres (DUBNER and HAYES 1979) as in the spinal cord.

The other ascending tracts are all situated in the ventrolateral column of the spinal cord. The important tracts are the following:
- the tractus spinoreticularis which ends in the medulla and from this region is relayed at the level of the medial thalamus (MEHLER, FEFERMAN and NAUTA 1960).
- the spinoreticulothalamic tract which has multiple relays in the formatio reticularis of the rombencephalon and mesencephalon and the dorsal lateral gray of mesencephalon and ends in the intralaminar nuclei of the thalamus.

Many neurons in the gigantocellular nuclei of the medulla and the pons are activated by noxious stimuli (KERR 1975). Stimulation of the neurons in this nucleus induces avoidance and flight behavior (WILSON 1974). The fibers of the spinoreticulothalamic tract or collateralis go to the subnucleus lateralis of the periaqueductal gray of the mesencephalon where an important descending modulatory system is present, as will be discussed further on.

More nuclei of the mesencephalon are involved in nociception. In the cat, noxious stimulation activates cells in the bulbomesencephalic regions (CONSEILLER et al. 1972). Before entering the thalamus the fibers of the spinoreticulothalamic tract divide into two groups: one runs dorsally to the already mentioned intralaminar nuclei and the other group passes more ventrally to the preoptic area and the lateral hypothalamic areas where the median mammillary nucleus is the head ganglion of the parasympathetic system. This may be responsible for the reactions accompanying noxious stimulation and pain, such as emptying the lower bowel and bladder with sudden severe pain.

The first tract is the paleospinothalamic tract which relays twice in the cord at the entrance of the peripheral nerves and in the cervical region. This tract terminates in the nucleus ventroposterior medialis of the thalamus (BOIVIE 1970).

The last ascending system is the previously mentioned neospinothalamic tract which terminates in the nucleus ventroposterior lateralis of the thalamus; this tract exists only in primates.

Specific afferents from the ventral, posteriolateral and medial nuclei

of the thalamus project to the third and fourth layers of the primary sensory area of the cortex (S I). This projection is topographically organized, i.e. every part of the body is represented at a defined spot in this cortical area. The cells of the intralaminar nuclei project to somatosensory cortex II (S II)(BURTON and JONES 1976).

S I is connected with regions in the motor cortex ipsilateral to S II and contralateral to S I and S II. S II projects only to S II in the contralateral hemisphere (BLOEDEL 1974). JONES and POWELL (1970) concluded that each primary sensory area projects to an adjacent field in the parietal cortex the output of which converges upon a region of the premotor frontal cortex.

Those thalamocortical fibers going more ventrally take the inferior thalamic peduncle to the orbital cortex of the frontal lobe and to the septal region; other fibers go to association areas of parietal, temporal and occipital lobes, including the basolateral amygdala and the putamen. Stimulation of the fornix and caudal part of the hippocampus induces conduct which is also seen after noxious stimuli. The amygdala is also involved in this process.

The most important advance in the last few years has been the discovery of stimulation-induced analgesia. Electrical stimulation of certain serotonergic neurons within the brain causes strong analgesia.

The regions where this stimulation is effective are those regions where many opiate receptors are present. Naloxone, a morphine antagonist, abolishes this stimulation-induced analgesia (BUCHSBAUM 1977).

Morphine acts on this system of neurons. In the rat such morphine-like analgesia has been obtained by stimulating the central gray of the midbrain.

The sites where morphine acts are the sites that induce analgesia. It is probable that the pathway is from the periaqueductal gray to the raphe nuclei and thence via a long tract to the posterior horn and inhibiting the neurons of lamina I and V of the spinal cord which are activated by noxious stimulation.

Besides the morphine-binding sites in the periventricular and periaqueductal gray, PERT and YAKSH (1974) found morphine-binding sites in the lower portion of the fourth ventricle along the aqueduct and possibly in the floor of the fourth ventricle. Two sites are also located near the

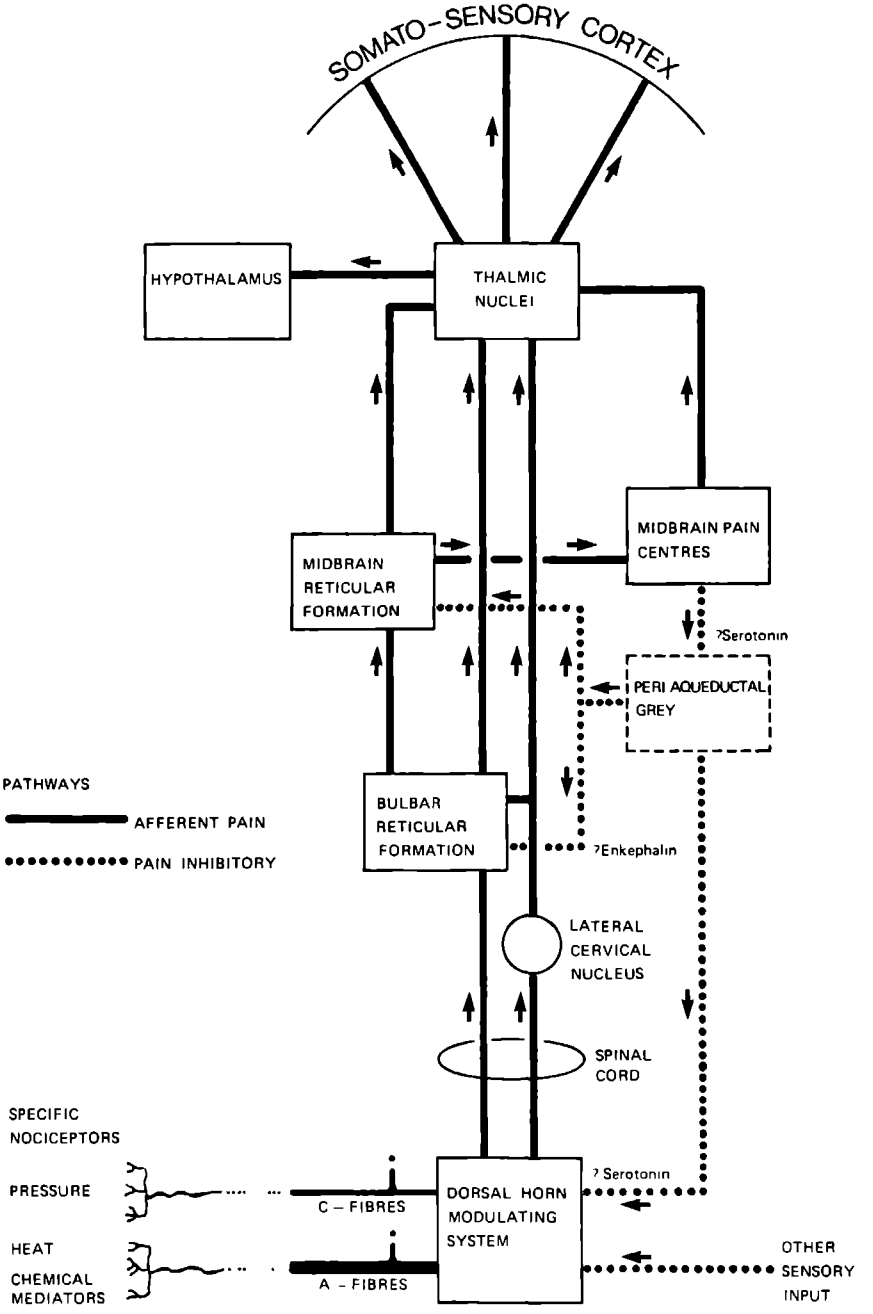

Fig. 1.1. The main pathways which appear to be involved in pain appreciation and analgesia in the cat (from: YOXALL 1978).

midline in the region of the subthalamic nuclei and in the vicinity of the thalamic intralaminar nuclear group.

With the discovery of endogenous opiate-like substances - endorphins - many new studies were undertaken. These endorphins are peptides that also bind to the opiate receptors, causing an endogenous pain relief. These endogenous opiate-like substances probably mediate the acupuncture analgesia and code for less pain-sensitive persons (BUCHSBAUM et al. 1981).

1.3. Pain measurement : a review

In experimental pain studies in both man and animals two problems are encountered. The first is the problem of the input i.e. the administration of pain stimuli controlled in both strength and duration.

The second is the controlled measurement of the intensity at which this input is experienced. In animals one speaks rather of nociception than of pain because the former term can be better defined.

1.3.1. Nociceptive stimulation

In pain research different kinds of stimuli are used. A good stimulus has to be reproducible, with fixed controlled intensities and minimal noxious effects to the tissue, and it has to be comparable with natural stimuli (LINEBERRY 1981).

The stimulus has to be noxious but not destructive to the tissues. On the basis of their nature the nociceptive stimuli can be divided into four groups:

a. mechanical stimuli
b. thermal stimuli
c. electrical stimuli
d. chemical stimuli

a) Mechanical stimuli are the oldest stimuli used in pain studies. There are qualitative stimuli, such as pricking the skin with a needle or forceps (OLIVERAS et al. 1974; NAKAMURA et al. 1980) and stimuli with variable intensity i.e. stimuli with controlled pressure (CLUTTON-BROCK 1961; DAVIDSON and NEUFELD 1974; FORGIONE et al. 1971). The advantage of mechanical stimuli is their natural quality, but it is difficult to control their intensity.

b) Thermal stimuli are often used in pharmacological tests. Examples of these tests are hot plates on which an animal is placed (FILIBECK and CASTELLANO 1974; PHAN et al. 1973) or dipping the tail in a hot water bath (DENNIS et al. 1980; GIARDINA et al. 1974; PHAN et al. 1973).

Radiant heat from a lamp focused on a small spot on the skin is also used (HARDY et al. 1952; HILL and AYLIFFE 1981; NAKAMURA et al. 1980; TULUNAY et al. 1975). More controlled intensities can be produced by a laser-emitted heat (MOR and CARMON 1975). Cold stimuli, such as ice-water, are also used for evoking pain (LASCELLES et al. 1974; HILGARD et al. 1974).

c) Mostly used in pain studies, however, are electrical shocks applied to the extremities by placing small animals on wire floors or by electrodes fixed to the skin (LI et al. 1975; BERKLEY and PARMER 1974; BONNET and PETERSON 1975; COOPER 1975; FLYNN et al. 1975; GRILLY and GENOVESE 1979; HARVEY and LINTS 1971; LYTLE 1975; PAALZOW 1975; STACHER et al. 1975; YAKSH and REDDY 1981).

A more refined technique is electrical stimulation of the tooth pulp (CHATRIAN et al. 1975; CHEN et al. 1981; FERRI et al. 1976; HOLMGREN 1975; HONGCHIEN 1976; MATTHEWS and SEARLE 1976; NAKAMURA et al. 1980). The tooth pulp has chiefly Aδ and C afferents.

Electrical stimulation has many advantages: it is reproducible, it has controlled intensities and it is easy to apply. The main disadvantage lies in the fact that it is not a natural stimulus.

d) Several drugs are used as chemical nociceptive stimuli. Among them are acetylcholine intraarterially (LIU 1974), formaldehyde i.a. (CLARK et al. 1935; DENNIS et al. 1980; LEVANTE et al. 1975), bradykinin i.a. (JEZDINSKY and HALEK 1974; MONCADA et al. 1975; NAKAMURA et al. 1980) or the intraperitoneal injection of acetic acid or phenylquinone in alcohol (NAKAMURA et al. 1980).

Dosage of the intensity and the duration of the stimulus is difficult except for bradykinin, which evokes pain for two minutes. Chemical stimuli give pain of long duration. They are used for induction of long lasting pain as in the induction of arthritis in rats by injection of paraffin oil with heat-killed *Mycobacterium butyricum* (DE CASTRO COSTA

et al. 1981).

For inducing chronic pain, spinal posterior rhizotomy or peripheral neurectomy (SWEET 1981) with spinal injection of tetanus toxin (KRYZHANOVSKY et al. 1981) seems indicated. In this connection, however, it is important to realise that in man the neural mechanisms which sustain chronic pain differ from those responsible for acute pain. Chronic pain has no physiological cause like acute pain in tissue damage. Chronic pain is a disease, it can exist without damage (COOPER et al. 1980).

Besides the fact that the intensity of pain is not controlled in this way, inducing chronic pain in animals also involves an important ethical problem.

In pain studies the use of electrical stimulation seems to be the best choice because a fine regulation of the intensity is possible. If the electrical stimulation is complemented with a mechanical or thermal stimulation which can be dosed in intensity and localisation, then all the characteristics of a good stimulus seem to be present.

1.3.2. Methods of 'pain' measurement

1.3.2.1. Autonomic and hormonal reactions

Only few studies have been carried out to investigate the influence of pain stimuli on autonomic and hormonal reflexes. Heart rate changes, changes in blood pressure, elevations in respiration frequency (DAVIDSON and NEUFELD 1974; HILGARD et al. 1974; MONCADA et al. 1975) and serum cortisol levels have been reported (LASCELLES et al. 1974; NABER et al. 1980). Respiration depth often increases after a pain stimulus. Changes in other parameters, however, are not specific pain reactions but increase in every acute stress or discomfort condition (DAVIDSON et al. 1974). Moreover there is no linear relationship between the intensity of the stimulus and the increase of these parameters.

1.3.2.2. Nociceptive reflexes and behavioral responses

Small rodents are often used in pharmacological tests for pain measurement. Reflex behavior such as tail withdrawal response after thermal stimulation or chemical stimulation in rats (DENNIS et al. 1980; PHAN et al.

1973; HILL and AYLIFFE 1981; NAKAMURA 1980) or in mice (GIARDINA 1974; TULUNAY et al. 1975) are approved techniques. The latency time between the application of the stimulus and the motor response is the measure of pain intensity. Another technique is the test in which mice or rats are placed on a heated plate. The heat of the plate can be controlled and the temperature which evokes paw-licking or jumping behavior is the pain threshold.

After administration of analgesics this threshold is elevated (PHAN et al. 1973; GIARDINA 1974; FILIBECK and CASTELLANO 1974). A comparable test is the jump-flinch technique in rats. Electrical foot shocks are administrated in increasing steps, at a certain intensity the rat starts a flinch response; this is the flinch threshold; at higher intensities the rat jumps: jump threshold (BONNET and PETERSON 1975; COOPER 1975; LYTLE 1975).

In electrical tooth pulp stimulation, in which steps of increasing current are administrated, the current which evokes the jaw-opening reflex (HONGCHIEN 1976) or a lip-licking response (FERRI et al. 1976) is the pain threshold.

Tail-flick, flinch and jump responses are spinal reflexes. Some authors use more 'affective-emotional' behavioral responses, such as paw licking, (vigorous) scratching, freezing or even selfmutilation, as indicators of pain sensations (DE CASTRO COSTA et al. 1981; JEZDINSKY and HALEK 1974; NAKAMURA et al. 1980; SWEET 1981; LINEBERRY 1981). DEWS (1974) stated that the analgesic effects of morphine in man cannot be controlled by monitoring of simple behavioral responses to painful stimulation and that the behavioral response is not a linearly increasing function of the intensity of painful stimulation, the relationship being much more complicated. A 'Bar-test', a nonpainful reflex test indicative of the normal activity of motor responses, has to be included in the experimental design to make sure that a muscle relaxant is not wrongly regarded as an analgesic agent (DENNIS et al. 1980).

1.3.2.3. Shock titration technique

The shock titration technique is a learned behavioral response. To one extremity an electrical stimulus is applied which increases in steps

of a few μA. The animal is taught to press a lever with another extremity or with its head so that the intensity of the stimulus decreases. When analgesics are given the animal will press the lever at a stronger current i.e. a higher pain threshold.

This technique has been used in rhesus monkeys (YASK and REDDY 1981) and rats (FLYNN et al. 1975). A disadvantage is that the animal will also learn to press the lever at lower intensities. Moreover in this technique also a motor response is used in pain reaction.

1.3.2.4. Signal detection theory

The first disadvantage of the former technique is not present in the signal detection theory. Series of two stimuli of different intensities, one painful and one not painful, are offered to a human being or an animal in an arbitrary fashion. The person or animal is taught to press a button or lever if the stimulus is painful and not to do this when it is not painful. If he presses the button after a painful stimulus it is a hit; if he presses the button after the nonpainful stimulus then it is false. The numbers of hits and falses have a gaussian distribution. After administration of an analgesic fewer hits will be scored. This technique is used in rats in such a way that the rat can choose between two chambers, each with a wire floor to which different stimuli are offered (GRILLY and GENOVESE 1979). The technique has also been used in primates (LINEBERRY et al. 1981) and in man (CHEN et al. 1981).

1.3.2.5. Verbal and vocal response

Only in man can the verbal report of what is painful and what not be obtained. In the oldest studies in man, and also in studies in which the effects of acupuncture are evaluated, this pain parameter is used (LI et al. 1975; CLUTTON BROCK 1961; HARDY et al. 1952; HOLMGREN 1975; PRICE and TURSKY 1975; STACHER et al. 1975; BUCHSBAUM et al. 1977). A scale of just noticeable differences has been made to quantify the pain sensation. For the subject, however, it is difficult to give an objective description of the pain sensations he feels when an increasing stimulus strength is given (MERSKEY 1973).

The signal detection theory is thus more reliable in human beings

(CHEN et al. 1981).

A few authors have used the intensity of vocalisations in animals as a measure of pain (PAALZOW 1975), or the stimulus intensity at which a squeak is evoked (GELLER et al. 1979). This stimulus intensity is then the pain threshold. True analgesics are capable of increasing the stimulus intensity at which the same squeak is evoked.

Vocal responses are not exclusively evoked by painful stimuli but also by nonpainful stimuli. Moreover the vocal response is not a conscious reaction, it can be evoked if certain structures of the thalamus are stimulated. Between species a very large difference exists between the stimulus intensities at which a squeak is evoked. In species with a very high threshold this method should not be used because too high stimulus intensities have to be employed.

1.3.2.6. Electrophysiological reactions to nociception

Stimulation of sense organs and of the skin leads to action potentials in peripheral nerves, spinal cord and brain structures. One stimulus evokes an action potential which is not visible in the electroencephalogram because the amplitude of this potential does not exceed the amplitude of the random noise of the EEG. DAWSON (1954) developed a photographic superimposition technique in which many electroencephalograms after a repetition of stimuli were projected on top of each other. The latency time - i.e. time between stimulus and appearance of the evoked action potential - is equal, so the evoked potential shows up.

Nowadays, however, an electronic summation technique is used, which makes the summated wave form of the evoked potential visible by canceling the random noise from the EEG. The resultant wave form is considered to represent the algebraic average of the evoked potentials after repetitive stimulation. The resultant response wave form is easily visible to the naked eye. This is one of the most important advantages of this method.

Another important property of this technique is the high confidence in the interference which results from the very nature of the average. Different time spans after stimulation can be used. Within these time spans more than one evoked potential is present. Electrical stimulation of the skin evokes four potentials in human central motor structures

with latencies of 25-40 msec, 80-100 msec, 120-160 msec and 220 msec (VADJA et al. 1980).

Many investigators have used this technique in human scalp recordings for pain measurement. The amplitudes of the later potentials with latencies greater than 50 msec are strongly related to the verbal report of pain experience in the subjects (BUCHSBAUM et al. 1977; NABER et al. 1980; ROHDEWALD et al. 1980). There is also a high correlation with the signal-detection hits score (CHEN et al. 1981).

This technique is also used to find those places in the thalamus where placement of stimulating electrodes can relieve chronic pain.

1.4. Outline of the present study

Many methods have been used for measuring nociception or pain in animals and man.

Of the above mentioned techniques autonomic and hormonal reactions cannot be used because they are more indicative of discomfort than of pain. Reflexes, which are often used for testing the depth of anesthesia, give us no information about the extent to which a nociceptive stimulus is experienced consciously. Behavioral responses can also be reduced by drugs acting on the motor centers of the brain and not affecting the sensory input, for example muscle relaxants.

The same disadvantage can be said to exist for the shock titration technique. Here it is also necessary to perform a motor response test. A very reliable technique is that based on the signal detection theory, but it is not easy to teach this to animals.

For this study we therefore chose the somatosensory evoked potential measurement. The magnitude of this response is correlated with the degree of pain experience in the verbal report of human subjects and also with the signal detection theory. It gives us information about the extent to which noxious stimulation is reaching the brain, but not about the appreciation of the noxious stimulation. If no impulses are reaching the brain (as demonstrated by a strong reduction in the evoked potentials) there is no noxious signal to be appreciated and good and reliable anesthesia and analgesia are present. If the somatosensory evoked potentials (SEP) are sampled in more than one brain structure the magnitude of the nociceptive information delivery to the brain can be

estimated.

On the basis of the above mentioned neurophysiological basis of nociception the SEP in the somatosensory cortex I and II both left and right, in the amygdala, in the hypothalamus, in the intralaminar nuclei of the thalamus and in the nucleus reticularis giganto cellularis of the reticular formation have been sampled.

In the experiments without anesthetics the nerve and spinal evoked potentials were sampled in order to obtain an idea about the origin of the different waves found in the SEP. In these experiments the intensity of the stimulus was also changed.

In the experiments with anesthetics the amplitudes and latency times of the potentials evoked by equal stimuli before and after administration of anesthetics were compared.

CHAPTER 2

MATERIALS AND METHODS

2.1. Introduction

Electrodes for recording of brain potentials were so placed that evoked potentials could be sampled from spinal, thalamic and cortical levels.

Recording of such potentials can be done in acute or chronic experiments; we chose chronic experiments because these require fewer animals (in the present study only eight). Another advantage is that no anesthetics are required during the recording sessions and the physiological condition is more nearly normal. Comparison between different anesthetics for use when the electrodes are implanted can be done separately in a single dog.

This chapter gives descriptions of the method of electrode implantation and of somatosensory stimulation and an outline of the experimental design.

2.2. Experimental animals

Beagle dogs were used for the following reasons:

a. Dogs have more differentiated brains than small rodents and rabbits.
b. Stereotactic procedures are possible because detailed stereotactic atlases are available.
c. The size of the animal is such that muscle relaxants can easily be injected intravenously and that tracheal intubation and artificial ventilation give no difficulties.
d. Wide experience with repeated anesthesization of dogs has been gained from veterinary medicine and laboratory animal experimentation.
e. Dogs are easy to handle and more resistant to surgical procedures than, for instance,cats.
f. The pharmacology of many anesthetics has been studied in dogs.

Eight male beagle dogs varying in age between 1½ and 2 years and weighing 12 - 15 kilograms were used for our experiments. They were housed individually on wire floors in cages measuring 1 x 2 meters.

Pelleted complete food[1]), 15-20 g/kg body weight per day, was given on 6 days a week.

2.3. Implantation of recording electrodes

2.3.1. In the brain

The dog was premedicated with droperidol[2]) and fentanyl[3]) 5 ml i.m., and atropine sulfate 0.1 mg/kg i.m.

Anesthesia was induced by intravenous administration of thiopental sodium[4]), 12 mg/kg. The dog was then intubated and anesthesia was maintained with a mixture of oxygen and nitrous oxide (1:2) and halothane[5]). During surgery the animal was artificially ventilated. Heart rate and temperature were continuously monitored. After shaving and disinfection of the skin of the head, the animal was placed in a stereotactic apparatus. A skin incision, 10 cm long, was made craniocaudally in the midline just between the ears. The periosteum was carefully scraped from the skull; 0.4 mm holes were drilled in the skull and 0.3 copper needle monopolar electrodes, insulated except for a length of 0.5 mm at the tip, were inserted.

Electrodes were placed, in accordance with the stereotactic atlas of LIM et al. (1960), in the somatosensory cortex I left and right, i.e. dorsal to the sulcus suprasylvius near the midline; in the somatosensory cortex II left and right, i.e. the gyrus sylvii posterior. Needle electrodes were also placed in the nucleus reticularis gigantocellularis of the reticular formation, left and right; in the hypothalamus left and right and two in the left amygdala as well as in the centrum medianum of the thalamus left and right. The coordinates are shown in Fig. 2.1. and table 2.1.

Both in the left and the right somatosensory cortex I two electrodes were placed, these were recorded one against the other. The same was done with the two electrodes in somatosensory cortex II, both left and right. In the nucleus reticularis gigantocellularis, in the thalamus and in the hypothalamus, the electrode on the left was recorded against that on the right. In the amygdala both electrodes were placed on the left side.

[1])Hope Farms; [2,3])Thalamonal®, Janssen;[4])Nesdonal®, Rhône Poulenc; [5])Fluothane®, I.C.I.

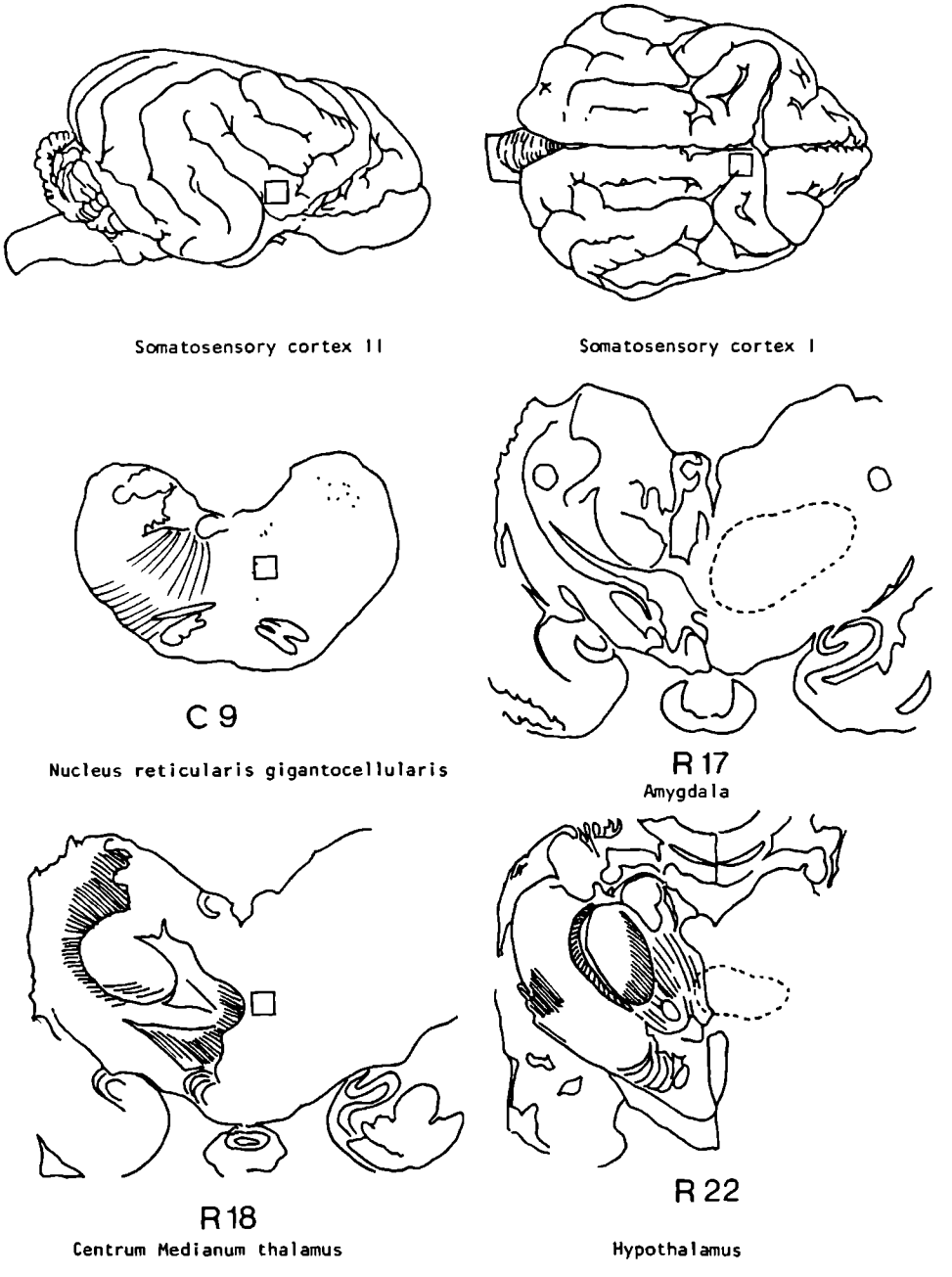

Fig. 2.1. Electrodes position in the dog's brain.

The electrode wires were soldered to gilded pins which fitted into a plug[6]). Two bone screws[7]), 2x ¼ mm were fixed in the skull. The plug was attached to the skull and to these bone screws with dental cement[8]).

Ampicillin[9]), 25 mg/kg was administered every other day for 10 days to prevent bacterial infections.

2.3.2. Around the sciatic nerve and in the spinal cord

An implantable electrode assembly consisting of cow skin and politef ('teflon') coated silver wire embedded in silicone rubber was developed, based on the design of NINOMIYA (1976). Teflon coated silver wire was attached to two pieces of tanned cow skin (5x7 mm). The two pieces were placed parallel at a distance of 10 mm and these electrodes were embedded together in silicone rubber in such a way that the cow skin was totally enclosed. A hole of 2x4 mm was then drilled perpendicularly through the cow skin pieces and one long side was cut open as far as this hole, so that the electrode could be opened for placing around a nerve (Fig. 2.2.).

The animal was again anesthetized as described under 2.1. An incision was made laterally in the right hind leg between the quadriceps femoris and semitendineus muscles. The sciatic nerve was dissected from the surrounding tissue, the electrode was placed around the nerve and the wires were led subcutaneously to the thoracolumbar region. Muscle and skin were then sutured.

Spinal cord

The dog was placed in sternal recumbency. A skin incision was made slightly lateral to the dorsal midline in the thoracolumbar region and the thoracolumbar fascia was incised immediately lateral to the spinous processes. The axial and hypaxial musculature was removed together with the periosteum from the last thoracic and first lumbar vertebrae. In each vertebra two holes were drilled in an oblique ventrolateral direction to the other side. Needle electrodes (0.3 mm) 12 mm long, insulated except for 8 mm from the tip, were inserted. Bone screws were installed and the electrodes were fixed with dental cement to these screws. The wires of these electro-

[6])Amphenol; [7])Parker kolon®; [8])Fastacryl®; [9])Albipen LA®, Mycofarm.

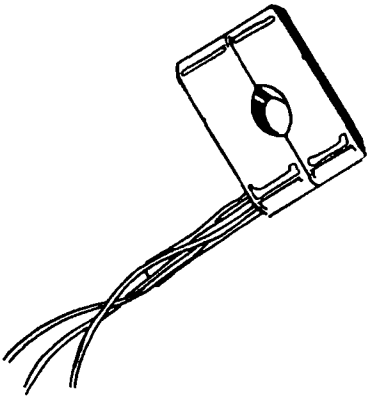

Fig. 2.2. Electrode assembly for recording of nerve potentials.

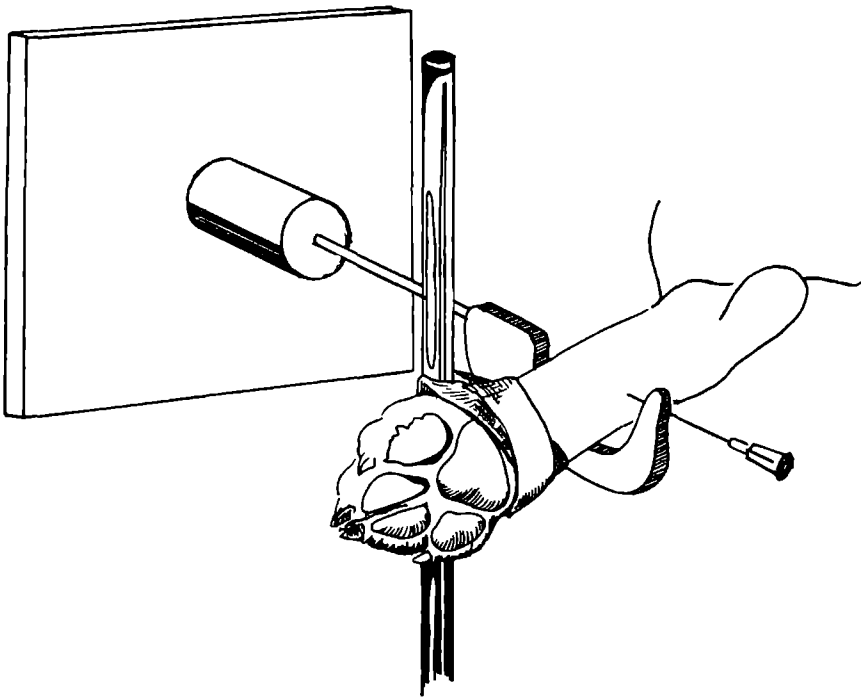

Fig. 2.3. *Mechanical stimulation* of the skin of the hindpaw in the dog.

des and of the sciatic nerve electrodes were also soldered to gilded pins. These pins were fitted into an amphenol connector which was sutured to the fascia and the skin. Ampicillin, 25 mg/kg, was given every other day for ten days to prevent bacterial infections. At least ten days elapsed before a dog was used for the first experiment.

2.4. Somatosensory stimulation

Various methods can be used for somatosensory stimulation (see Chapter 1). Three different methods were used in the present study, primarily electrical stimulation of the hind paw and mechanical stimulation of the skin of the hind paw. The hind paw was used because nerve action potentials could be recorded easily. Both these stimuli were used in 'blank' and 'anesthetic' experiments. In one experiment only, electrical stimulation of the canine tooth pulp was also used. This was done for comparison of the potentials evoked by these three methods.

2.4.1. Mechanical skin stimulation

As mechanostimulator the to-and-fro movements of an electrodynamic loudspeaker were used (BURCHARD et al. 1967). To the center of this loudspeaker one end of a metal pin was fixed with adhesive. One end of a half-ring with a diameter of 5 cm was screwed to the other end of the metal pin. In the other end of the half-ring a hole was drilled into which a needle could be fixed with a screw. Movement of the conus of the loudspeaker gave traction on the needle in such a way that the needle pricked into the skin. The loudspeaker was built into a box. At the place where the metal pin emerged a massive plastic cone with a hole in the middle was glued. The metal pin could slide up and down through this hole, which resulted in a better stabilization of the needle (Fig. 2.3.).

With a Grass S 88 stimulator and an amplifier rectangular pulses of 1-10 volts with a duration of 1-40 msec were delivered to the loudspeaker. In this way the force with which the needle was moved and the distance over which it moved could be exactly regulated.

In Fig. 2.4. the force with which the needle was moved is shown in relation to the voltage and stimulus duration.

The hind paw of the dog was fixed in such a way that the needle pricked the volar side of the metatarsal part of the leg; at the higher intensity

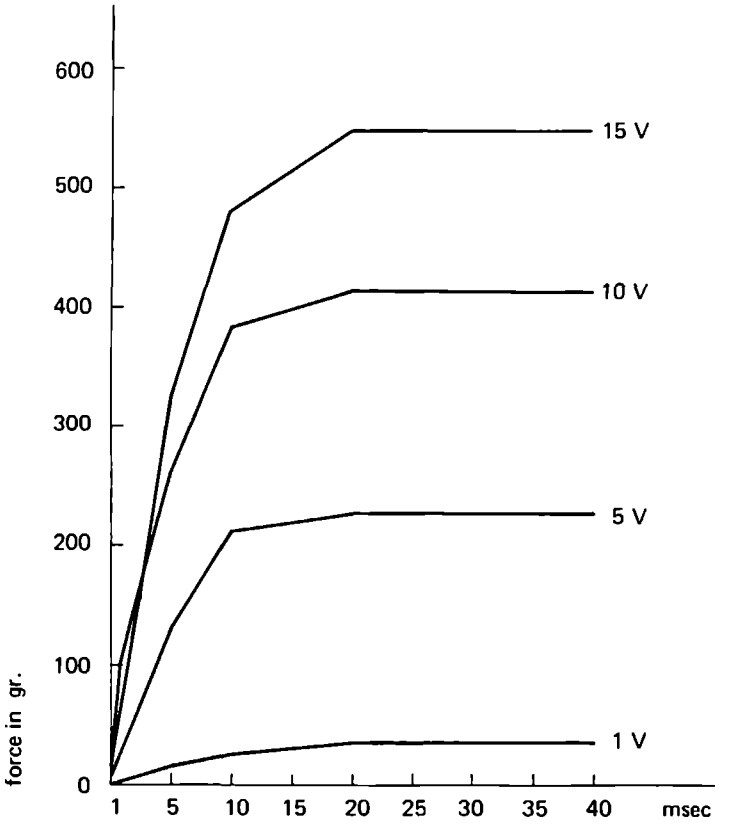

Fig. 2.4. Relationship between power delivered to the loudspeaker and force evoked by this stimulation.

the hypodermic needle actually penetrated the skin.

2.4.2. Electrical skin stimulation

Two round cottonwool electrodes with a diameter of 8 mm held in a metal cup were used. The electrodes were fixed in plastic with their centers 23 mm apart (Fig. 2.5.).

The cottonwool was moistened with saline solution and electrode paste was applied. The electrode then was pressed onto the plantar surface of the right hind paw just proximal to the sole. The skin was shaved and degreased with 96% alcohol. The resistance of the electrode decreased gradually over ten minutes and stabilized at about 50 kΩ. Via a Grass S 88 stimulatior rectangular pulses of 1-70 constant voltage and with a duration of one msec were delivered to this electrode.

2.4.3. Electrical tooth pulp stimulation

In the right upper canine two holes were drilled in the enamel as far as the dentin. The holes were 5 mm apart and had a diameter of 1.2 mm. Two copper electrodes with a diameter of 1 mm fixed in plastic, also at a distance of 5 mm were placed in the holes (Fig. 2.6.). The resistance was lowered by application of electrode paste. To prevent leakage of current to the gingiva the tooth and the surroundings were kept as dry as possible with cottonwool. Stimulation of the canine tooth pulp was performed only once in each dog. After the experiment the holes in the tooth were filled with amalgam. The resistance was 150 kΩ. With a Grass S 88 stimulator and an insulator, a voltage of 220 volt and a stimulus duration of 1 msec was given. This corresponds to a current of 1.5 mA, which is in accordance with the intensities used in humans (CHATRIAN et al. 1975) and in dogs (CHIN and DOMINO 1961).

2.5. The experimental design

Each dog was used at least twenty times. Between two experiments it was allowed at least one week rest.

2 mg of pancuronium bromide[10)] was injected with a butterfly

[10)] Pavulon®, Organon International.

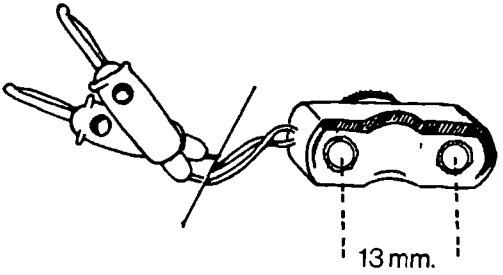

Fig. 2.5. Electrode assembly for *electrical stimulation.*

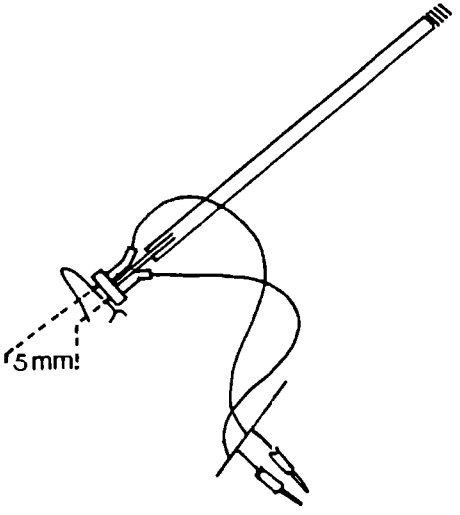

Fig. 2.6. Electrode for *electrical tooth-pulp stimulation.*

needle which was inserted into the vena cephalica and fixed with adhesive tape to the skin. An endotracheal tube lubricated with lidocaine-containing ointment was placed in the trachea immediately after the injection of pancuronium. The tube was then connected to an artificial ventilator. The frequency and volume of respiration were regulated in such a way that the carbon dioxide content of the expired air was kept between 5.0 and 5.3% i.e. a physiological condition (BERGER et al. 1974). A capnograph (Mark II Godart) was used for this purpose.

The dog was placed on a heated mattress (temperature 38°C) and covered with a blanket to prevent hypothermia. An electrocardiogram was recorded and an infrared light plethysmogram was monitored for control of the peripheral circulation. The amphenol plugs were connected to electroencephalographic amplifiers (van Gogh HRP - 0/8 2b).

The time constant was set at 0.3 sec and the high-frequency filter at 100 Hz. The evoked potentials were led to an averager (Hewlett Packard 548 8A) to reduce the background signal noise (of about 60 μV) and to show up the evoked potentials (of about 10-400 μV). The stimulation devices were attached as described above. All stimuli used were produced by a Grass S 88 stimulator which gave a trigger pulse to the averager at the same time as the impulse was delivered to the stimulation devices. During a period of 500 msec after the stimulus the potentials from the recording electrodes were fed into the 'memory' of the averager. One second later the same procedure was followed. The averager computed the mean of the 2 potentials. In this way 64 potentials were computed. The background noise in the signal was reduced to zero while the stimulus-evoked potential emerged. These 64 averaged potentials were photographed. The peak latencies of the potentials in msec and the peak-to-peak amplitudes in μV were measured electronically with an x-y coordinate-measuring device and stored in a computer.

Two series of experiments were performed

1. Experiments in which anesthetics were administered. Here only brain potentials were recorded and a stimulus with constant intensity and duration both before and after administration of the anesthetic was used. The influence of the anesthetic on the amplitude and the latency time of the evoked potentials was studied.
2. After termination of this series of experiments the nerve and spinal cord recording electrodes were implanted, after which a series of

blank experiments without anesthetics was carried out. The strength and duration of the stimulus were varied and the amplitudes and latencies of the evoked potentials in nerve, spinal cord and brain were recorded.

After these experiments the dogs were sacrificed and the placing of the electrodes was checked histologically.

We wish to point out that the stimulus intensity used by us was well below the pain-tolerance limit as reported in the literature (GOLDBERGER and TURSKY 1976). This tolerance limit was, moreover, established in animals which were neither paralysed nor anesthesized, making it possible to choose a stimulus intensity well below the tolerance limit in question.

As is usual in experiments of this kind, the dogs were allowed to become accustomed to the experimental conditions.

Table 2.1. Coordinates of recording electrode positions according to the atlas of LIM et al. (1960) in mm

	Left				Right			
brain structures	FR / C		lat.	dorsal	FR / C		lat.	dorsal
somatosensory cortex I	27 30		4 4	just through dura	27 30		4 4	just through dura
somatosensory cortex II	25 30		17 17	20 20	27 30		17 17	20 20
nucleus reticularis gigantocellularis		9	2	3.5		9	2	3.5
intralaminar thalamus	18		3	12	18		3	12
hypothalamus	22		3	10	22		3	10
amygdala	17 22		12 13	9 5				

CHAPTER 3

THE SOMATOSENSORY EVOKED POTENTIAL IN DOGS WITH REFERENCE TO NOCICEPTION

3.1. General introduction

If an external stimulus is administered to a peripheral nerve, a potential can be recorded in nervous structures. This potential is often so small that it is masked by the spontaneous electrical activity of the brain, which has greater amplitudes. Electronic summation of numerous stimuli flattens the background activity and the potentials following somatosensory stimulation become visible (CLARK et al. 1961). Both spontaneous and stimulus-evoked potentials are synchronous electrical discharges of a number of neurons; the greater this number the greater the amplitude of the evoked potential.

One somatosensory stimulus evokes more than one potential in the brain; these potentials appear at different times after the stimulus and have different latency times.

It is likely that the potentials with different latency times are evoked by stimulation of peripheral nerve fibers with different conduction velocities. It is also likely that as more fibers are stimulated, i.e. the stimulus becomes stronger, the amplitudes of these evoked potentials will increase. As soon as the stimulus becomes so strong as to be noxious the nociceptive fibers are especially stimulated.

Aδ and C fibers, involved in nociception, are abundantly present in tooth pulp, and electrical stimulation of the tooth pulp evokes mainly nociceptive reactions (BIEDENBACH et al. 1979). This chapter presents a comparison of potentials evoked by electrical stimulation of the tooth pulp with those evoked by electrical and mechanical stimulation of the skin. The numbers and latencies of the potentials evoked by these three different methods are presented.

Different intensities of skin stimulation, both electrical and mechanical, were used to determine the nociceptive threshold, and this was correlated with the amplitude of the potentials.

In accordance with what is known of the neurophysiological basis of pain, as reviewed in Chapter 1, we have recorded the potentials in the various nervous structures from peripheral to central; in this way evoked

potentials recorded in the sciatic nerve and spinal cord, nucleus reticularis gigantocellularis, intralaminar thalamic nuclei, hypothalamus, amygdala (left) and somatosensory cortex I and II (both left and right) are compared.

The importance of these different structures in nociception, the path of the nociceptive impulses through the brain and the origins of the different potentials are discussed also in comparison with the evoked potential found in humans and in animals by other investigators. The data obtained in this way are used to determine the nociceptive intensities of both electrical and mechanical skin stimulation.

The experiments were carried out according to the methods described in Chapter 2.

3.2. Evoked nerve and spinal potentials

3.2.1. Introduction

Afferents are classified as Aα , Aβ , Aγ , Aδ and C-fibers according to their myelination and their conduction velocities. Aα and Aβ fibers are thick, myelinated, fast-conducting fibers between 30 and 60 m/sec and are involved in tactile stimuli (BOUREAU et al. 1978).

The slowest-conducting fibers in the Aβ and Aγ groups have facilitatory effects on the Aδ and C fibers (WILLER et al. 1980). They also react to temperatures above 45°C (BECK et al. 1974). Aδ are the slowest-conducting myelinated fibers; their conduction velocity lies between 2.5 and 15 m/sec. They are activated by innocuous and noxious stimuli. Needle pricks (BOUREAU et al. 1978; BURGESS and PERL 1967) and noxious heat activate these fibers (IGGO and OGAWA 1971). C fibers are nonmyelinated, very slow-conducting fibers with a conduction velocity of 0.5-2.5 m/sec (MEYER and CAMPBELL 1981). Most of these fibers are polymodal, i.e. they fire after different kinds of stimulation (BESSOU and PERL 1969). They are, however, sensitive to noxious thermal stimulation and are therefore responsible for burning pain (CLARK et al. 1935; TOREBJÖRK and HALLIN 1973). They also react to intense mechanical noxious stimulation (IGGO and OGAWA 1971; TOREBJÖRK; IRIUCHIJIMA and ZOTTERMAN 1960).

Two methods of stimulation have been used in our experiments, mechanical stimulation with a hypodermic needle and electrical stimulation. Elec-

trical stimulation can be compared with thermal stimulation, as will be discussed in the following pages.

Two different mechanical intensities, 150 and 450 grams pressure, and three electrical intensities, 10, 40 and 60 volts, were used in six dogs. The distance between stimulation site and recording site was about 20 cm for sciatic nerve recording and about 35 cm for spinal cord recording.

3.2.2. Results

From the recorded latency times of the potentials found in the sciatic nerve, the conduction velocities of these potentials were computed. The mean of the amplitudes of the evoked potentials in six dogs was also computed. This was done for each stimulus strength. The mean of these amplitudes of the mechanically evoked nerve potential with different conduction velocities is shown in Fig. 3.1. Only one peak in the Aβ range, two peaks in the Aγ range, three in the Aδ range and one in the C fiber range were present.

The same stimulation evoked potentials in the spinal cord, as demonstrated in Fig. 3.2. The means and standard deviations of the latency times (horizontal bars) and the means and standard deviations of the amplitudes (vertical bars) of the evoked potentials are given. Six peaks were present in this evoked response, with successive latencies of 10, 15, 28, 64, 98 and 142 msec.

Electrical stimulation of the skin evoked a potential in the sciatic nerve at a distance of 20 cm as demonstrated in Fig. 3.3. Here the conduction velocities were computed from the latency times; one peak in the Aβ range, one in the Aγ range, three in the Aδ range and one in the C fiber range were present. Six peaks were also present in the spinal electrically evoked potential (Fig. 3.4.). In both the nerve and spinal cord the amplitudes, especially of the C fiber and Aδ fiber evoked potentials increased as stimulus intensity increased.

3.2.3. Discussion and conclusion

As seen from the results, both electrical and mechanical stimulation activate the same fibers in the sciatic nerve and evoke in the spinal cord potentials with almost the same latencies. At least six peaks in the

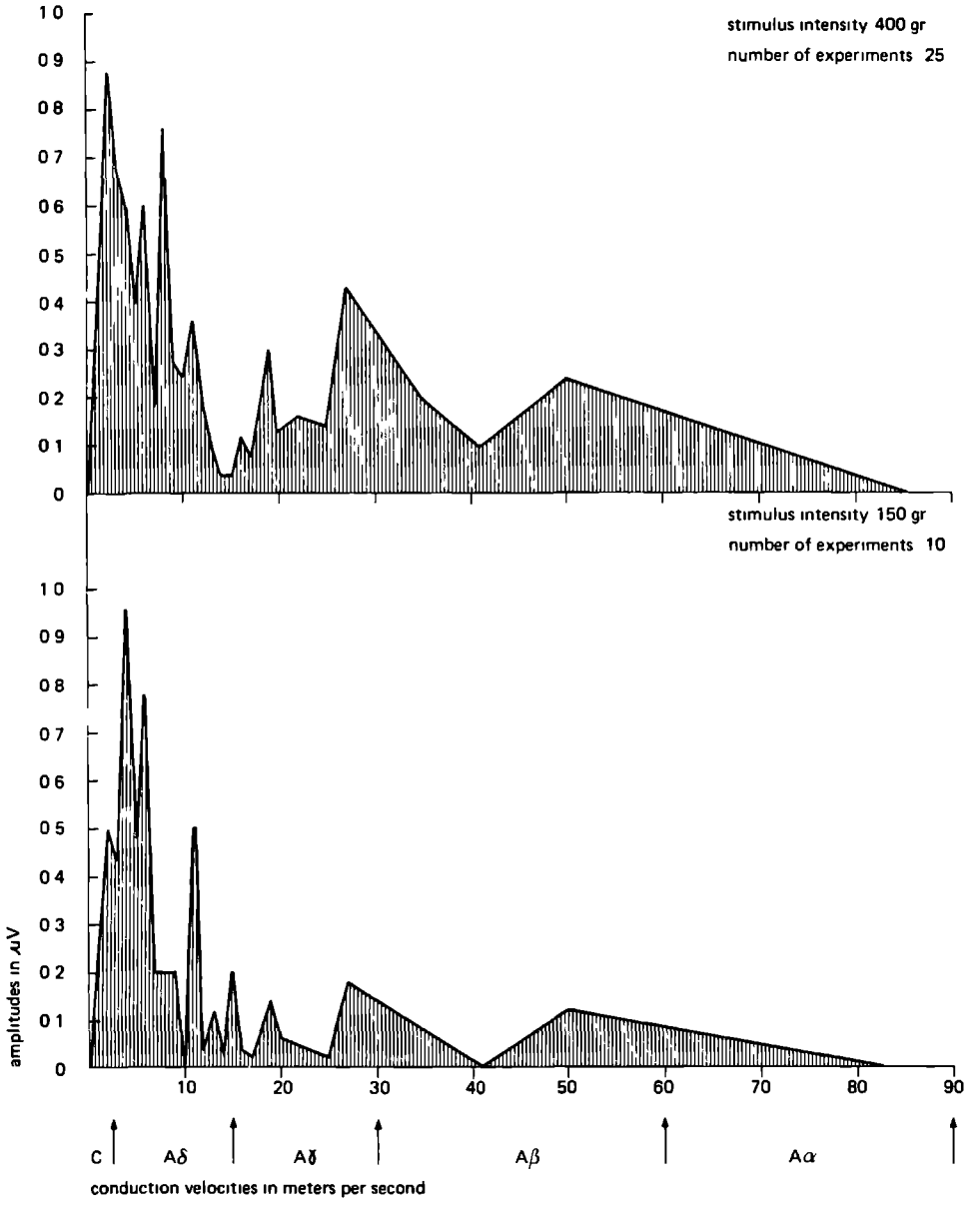

Fig. 3.1. Nerve evoked potentials after *mechanical* skin stimulation. Amplitudes and conduction velocities in sciatic nerve after *mechanical* stimulation of the skin at two different stimulus intensities.

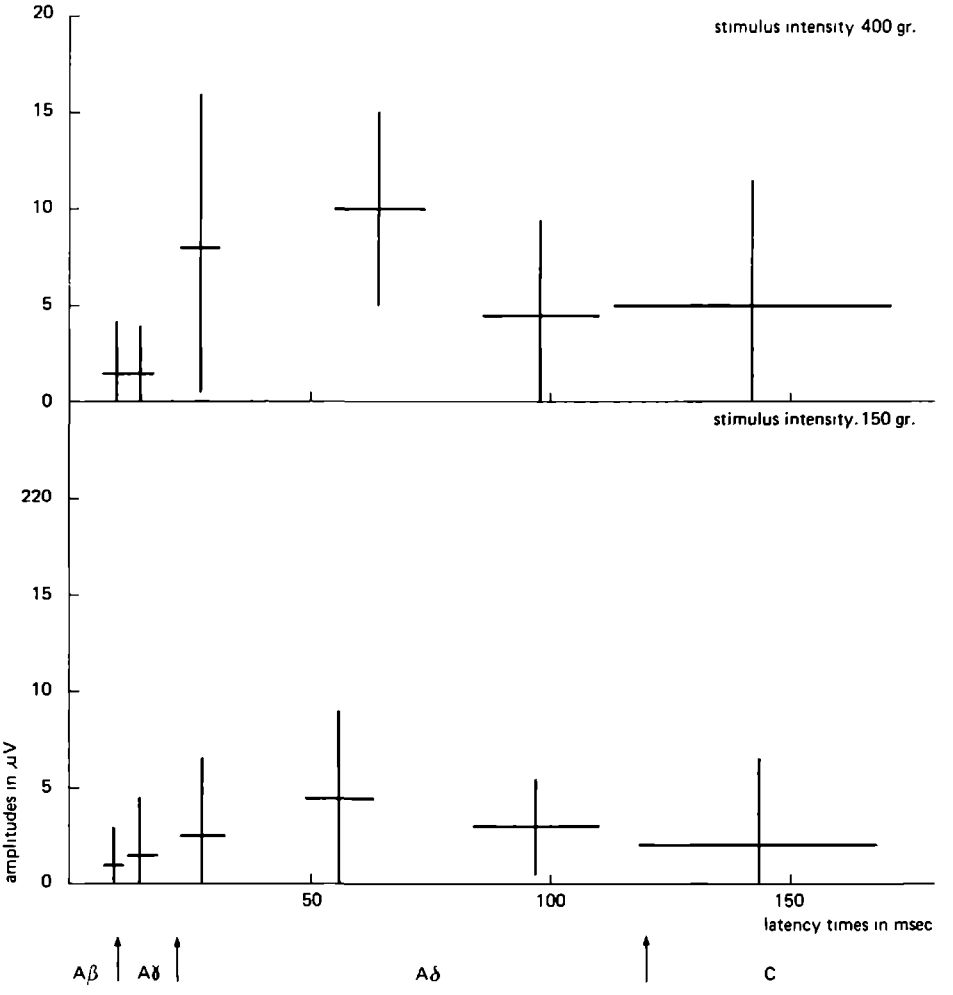

Fig. 3.2. *Mechanically* evoked potentials in spinal cord; mean and standard deviations of amplitudes (vertical bars) and latency times (horizontal bars) of peaks in spinal *mechanically* evoked potentials at two different stimulus intensities.

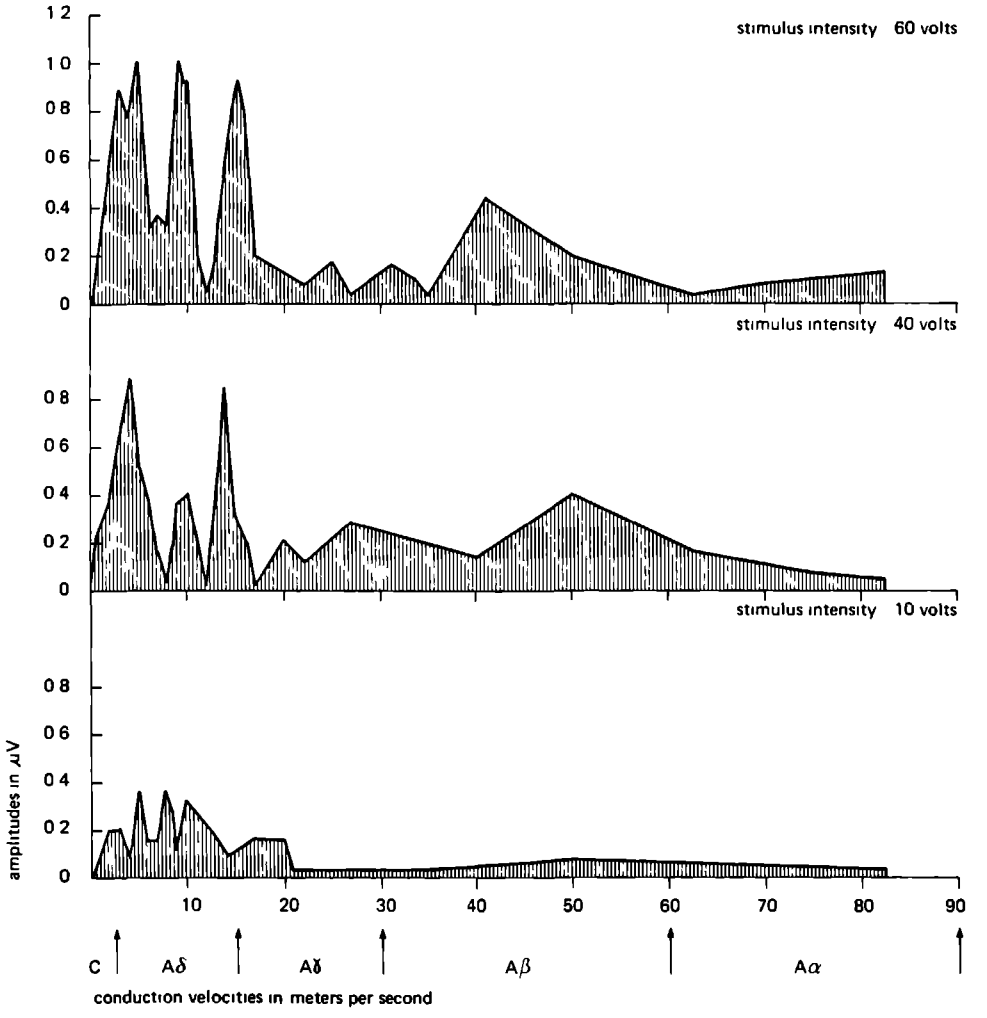

Fig. 3.3. Nerve evoked potentials after *electrical* skin stimulation. Amplitudes and conduction velocities of sciatic nerve potentials after *electrical* stimulation of the skin at increasing intensities.

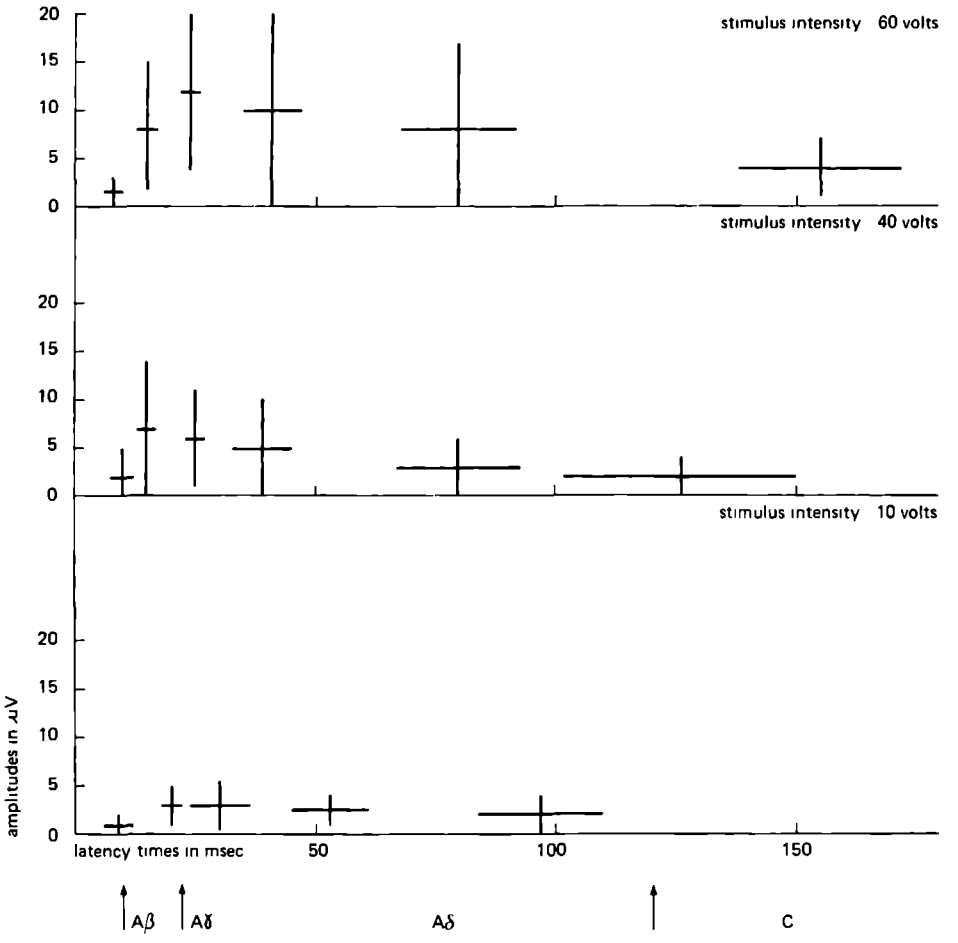

Fig. 3.4. *Electrically* evoked potentials in spinal cord; mean and standard deviations of amplitudes (vertical bars) and latency times (horizontal bars) of peaks in spinal *electrically* evoked potentials at three different stimulus intensities.

nerve were found: one in the Aβ range, one in the Aγ range, three in the Aδ range and one in the C fiber range. Six peaks were also present in the spinal cord. The distance between stimulation and recording sites for the spinal cord was 35 cm. This means that stimulation of Aβ fibers evokes a potential between 0 and 10 msec, stimulation of Aγ fibers between 10 and 20 msec, stimulation of Aδ fibers between 20 and 120 msec and stimulation of C fibers a peak larger than 120 msec. In the spinal evoked response six peaks were present. The first one was probably Aβ fiber-evoked, the next one Aγ fiber-evoked. These peaks remained fairly stable as the stimulus intensity increased. The next three peaks were evoked by Aδ fiber stimulation and their amplitudes increased as the intensity of the stimulus increased. The same can be said of the last peak, a C fiber evoked potential. The mean of the amplitude of the Aβ range potential in the nerve was larger after electrical than after mechanical stimulation. For the C fiber potential the opposite was seen.

In general the Aδ and C fiber potentials had the largest amplitudes both in nerve and in spinal cord, and increased the most as stimulus intensity increased. The highest intensities are painful in character, but below tolerance threshold. The mechanical stimulation actually injures the tissue by penetrating the skin, and stimulates the Aδ and C fibers more and more as the intensity of the stimulus increases. The electrical stimulation can be compared with thermal stimulation by equating the energy of the two stimulation methods.

Electrical stimulation evokes a power of $\frac{V^2}{R}$ joule/sec. With 20 volt and 1 msec this is $\frac{400}{50} \times 0.001 = 0.008$ joule. 8 J is applied for 1 second. The stimulation area with this electrode is approximately 5 cm^2, corresponding to 1.3 J per cm^2/sec. This is above the thermal threshold of HARDY et al. (1952) (1.046 J/cm^2/sec) and the threshold of CARMON et al. (1976) (0.836 J/cm^2/sec). PROCACCI et al. (1974), however, report a threshold of 4.184 J/cm^2, which means, for our electrode, $\sqrt{5 \times 4,184 \times 50} = 32$ volt. MOR and CARMON (1975) found in human subjects a supramaximal painful thermal stimulus, i.e. just above the tolerance threshold of 11 J/cm^2/sec. This stimulation also produces a slight erythema. For our electrode it corresponds to 112 volt, so with 60 volt we stimulated above the pain threshold but below an actual tissue destruction. From the height of the amplitudes it seems that the

electrical stimulation is stronger than the mechanical stimulation. It can be concluded that the high intensities of both the stimulation methods activate the Aδ and C fibers which are involved in nociception, and that the stimulation is painful but below tolerance threshold.

3.3. Central pain system

3.3.1. Subcortical structures

Many subcortical structures are involved in nociception. In accordance with neurophysiological bases of nociception, as reviewed in Chapter 1, the following structures were chosen: the nucleus reticularis gigantocellularis, the intralaminar nuclei of the thalamus, the hypothalamus and the amygdala.

3.3.1.1. The nucleus reticularis gigantocellularis (NRGC)

3.3.1.1.1. Introduction

Many of the fibers from the spinal cord which are involved in nociception terminate or have collaterals in the reticular formation (BOWSHER 1975). Especially the dorsal aqueduct and the periaqueductal gray matter of the midbrain are pain-involved brain centers. LeBLANC and GATIDON (1972) found in the medulla oblongata of decerebrated cats many neurons which reacted to peripheral painful stimuli. Neurons of the nucleus reticularis gigantocellularis (NRGC) were activated primarily by nociceptive stimuli and each neuron was responsive to stimulation of large discontinuous areas of the body, face or both.

The nucleus reticularis gigantocellularis (NRGC) is involved in

(a) processing of diffuse pain sensations

(b) elaboration of affective reactions to pain and

(c) sensomotor integration

(PEARL and ANDERSON 1976).

3.3.1.1.2. Results

For the peaks present in the NRGC evoked potentials after painful tooth-pulp stimulation the means and standard deviations of both the amplitudes and the latency times are presented in Fig. 3.5.

Four peaks with mean latency times of 27 msec, 70 msec, 135 msec and 308 msec were found. The highest amplitudes were seen in the 70, 135 and 308 peaks. The *mechanical* needle prick stimulation evoked potentials with four peaks (Fig. 3.6.). The mean latencies of these peaks were 15, 40, 90 and 225 msec. The amplitudes of the last three peaks were the largest; the first one was very small. The amplitudes increased as the intensity of the needle prick increased.

Electrical stimulation of the skin of the hindpaw-evoked potentials in the NRGC with 5 peaks (Fig. 3.7.). These peaks had mean latencies of 20, 35, 75, 140 and 260 msec. The amplitudes increased as the voltage of the stimulus increased and were highest in the last three peaks.

3.3.1.1.3. Discussion and conclusion

OLESON and LIEBESKIND (1976) found evoked potentials in the central gray of the rat after noxious mechanical hind paw stimulation with peaks at 10 msec, 12 msec, 15 msec, 20 msec and 60 msec. If the size of a rat is compared with that of a dog it is reasonable to conclude that the impulse has to be conducted over a distance 4 times as long as in the dog. If the latencies found by these investigators are multiplied by this factor, the latencies found in our experiments are in agreement.

Comparison of the peak latencies of the potentials evoked by the three stimulation methods gives the following congruences: the needle-evoked peak with a latency of 15 msec corresponds to the electrically evoked peak with 20 msec latency; the 27 msec peak in the tooth-pulp-evoked wave to the 40 msec needle peak and the 35 msec electrically evoked peak. The 70 msec peak of the tooth-pulp-evoked potential corresponds to the 90 msec peak of the needle-evoked potential and to the 75 msec peak of the electrically evoked potential. The 135 msec peak in the tooth-pulp-evoked response corresponds to the 225 msec peak in the mechanically evoked response and the 140 msec peak in the electrically evoked potential and the 308 msec peak of the tooth-pulp-evoked potential to the 260 msec peak in the electrically evoked potential. Because a smaller distance from peri-

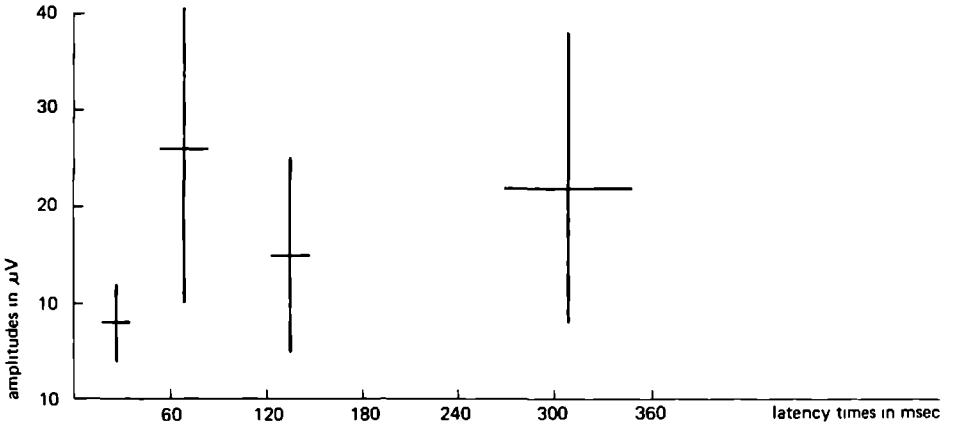

Fig. 3.5. Mean and standard deviations of amplitudes (vertical bars) and latency times (horizontal bars) of peaks found in nucleus reticularis gigantocellularis after *electrical tooth-pulp* stimulation.

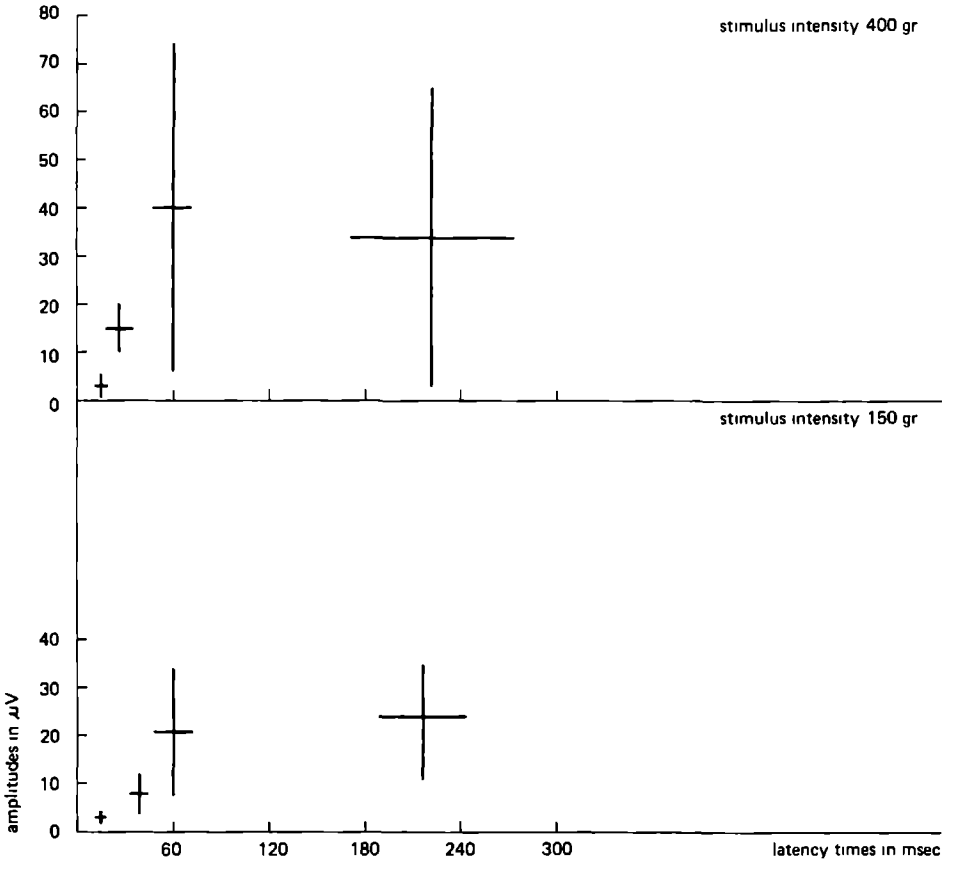

Fig. 3.6. Mean and standard deviations of amplitudes (vertical bars) and latency times (horizontal bars) of peaks in *mechanically* evoked potentials in the nucleus reticularis gigantocellularis at two different stimulus intensities.

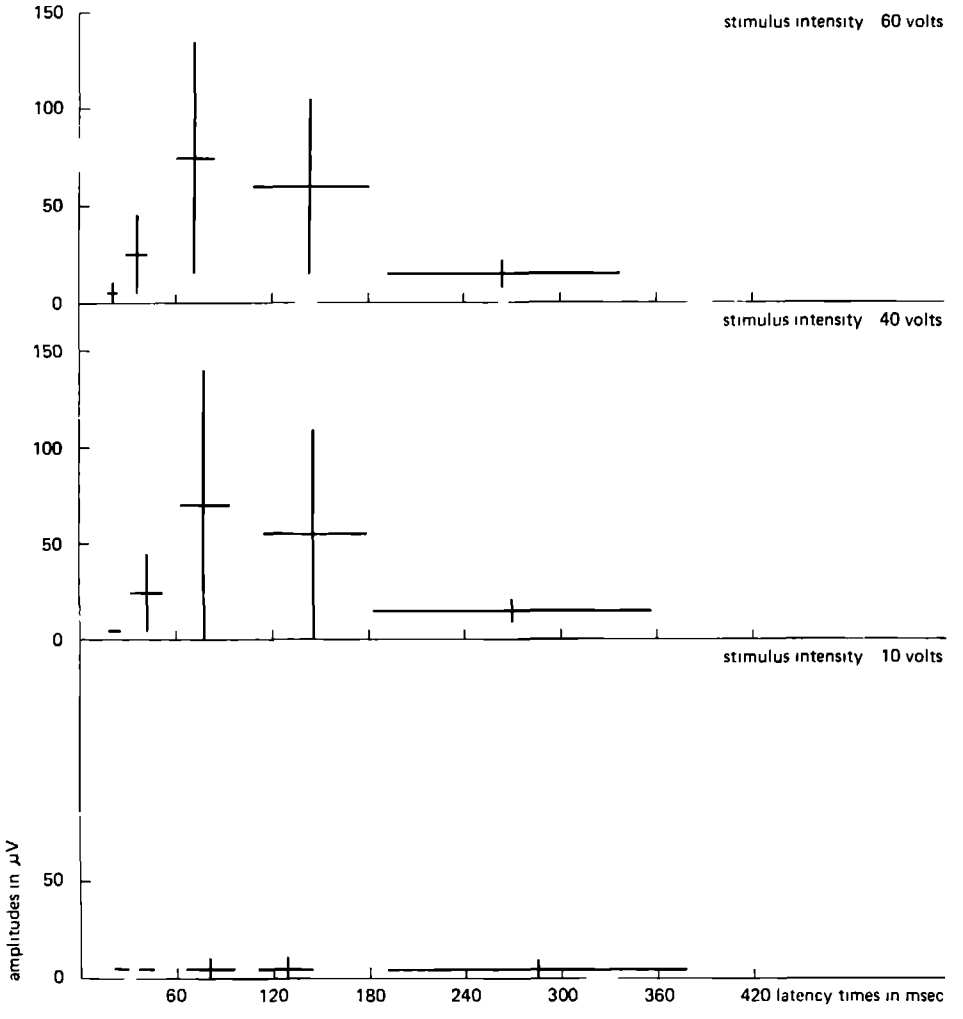

Fig. 3.7. Mean and standard deviations of amplitudes (vertical bars) and latency times (horizontal bars) of *electrically* evoked potentials in the nucleus reticularis gigantocellularis at three different stimulus intensities

phery to brain has to be covered in tooth-pulp stimulation than in stimulation of the hind paw, the latencies of the tooth-pulp-evoked potential are shorter.

The later components in the needle-evoked potential have some longer latencies. This is probably due to a longer time between starting the stimulus and the pricking of the skin. The needle has to be moved over a distance.

If the peak latencies found in the spinal cord are compared with these results, it seems that the 70-90 msec peaks are evoked by Aδ fiber stimulation and the 135-225 msec peaks by C fiber stimulation.

The very late waves in the tooth pulp potential (peak latency 308 msec) and electrically evoked potential (peak latency 260 msec) probably represent potentials which are generated in the brain itself as a response to the nociceptive stimulation. At any rate, the magnitude of the amplitude pleads for a strong involvement of the 70-90 and 135-225 peak in nociception. The peaks with these latencies increase in amplitude as stimulus intensity increases. The NRGC in dogs is involved in nociception, the Aδ and C fiber evoked potentials have a larger amplitude in this nucleus and the amplitude increases as stimulus intensity increases.

3.3.1.2. The thalamic intralaminar nuclei

3.3.1.2.1. Introduction

As stated in the first chapter, large parts of the thalamus are involved in somatosensory perception. The thalamus receives input from the midbrain and sends axons to the sensory cortex (DONALDSON et al. 1975).

BOWSHER (1975) coagulated those parts of the midbrain where the highest evoked potentials after stimulation of the extremities in cats were found. At autopsy neuron degeneration was seen in the following diencephalic centers: posterior nuclei group, centrum medianum, nucleus centralis lateralis and ventrobasal thalamus. The majority of the neurons in these nuclei also respond to noxious thermal stimuli (PESCHANSKI et al. 1980).

ISHIJIMA et al. (1975) report that the neurons in the central median parafascicular complex have very wide fields and that electrical stimulation of these intralaminar nuclei in humans causes burning pain in a

wide area of the body contralaterally or sometimes even bilaterally. Most axons of intralaminar cells are richly collaterized, producing an abundant interconnective substratum for interaction with adjacent, non-specific and specific nuclear pools (SCHEIBEL and SCHEIBEL 1967).

In primates the ventroposterior lateral nucleus of the thalamus is also an important relay station in nociception (PEARSON and HAINES 1980).

The nuclei of the ventroposterior part of the thalamus are, in contradistinction to the intralaminar nuclei, topographically organized, i.e. parts of the body are represented in different nuclei (NATHAN 1977).

Such anatomical and electrophysiological studies have formed the basis for neurosurgical procedures. Several investigators have tried to relieve chronic pain by coagulation or electrical stimulation of these thalamic structures. Coagulation of the nucleus ventrocaudalis parvocellularis and nucleus limitans elicited pain relief in the beginning, but unfortunately relapses occurred (MUNDINGER 1974). COOPER et al. (1980) noted pain relief after electrical stimulation of the thalamus with depth electrodes, but this also gave improvement of hemiparesis, dystonia, torticollis and tremor. The thalamus is important in pain perception. The suppression of pain originating from large areas of the body by application of innocuous stimuli to the affected or unrelated parts, or by dorsal column and peripheral nerve stimulation, might be explained in part by wide somatic convergence and inhibitory mechanism in the somatic response of the thalamic posterior group of nuclei (DONG and WAGMAN 1976). According to ALBE-FESSARD and FESSARD (1976) this might also be the mechanism by which acupuncture analgesia acts.

The role of the thalamus in pain perception is probably to reinforce the emotional aspects of pain. From the foregoing it can be concluded that in dogs the intralaminar nuclei are more important than the ventroposterior lateral nucleus. Therefore the intralaminar nuclei of the thalamus were chosen for nociceptive evoked recording.

3.3.1.2.2. Results

Electrical tooth-pulp stimulation evoked a potential with six peaks. The means of the latencies of these peaks were 30, 46, 79, 130, 211 and 365 msec (Fig. 3.8.). The amplitudes of the later components were greater than those of the early ones.

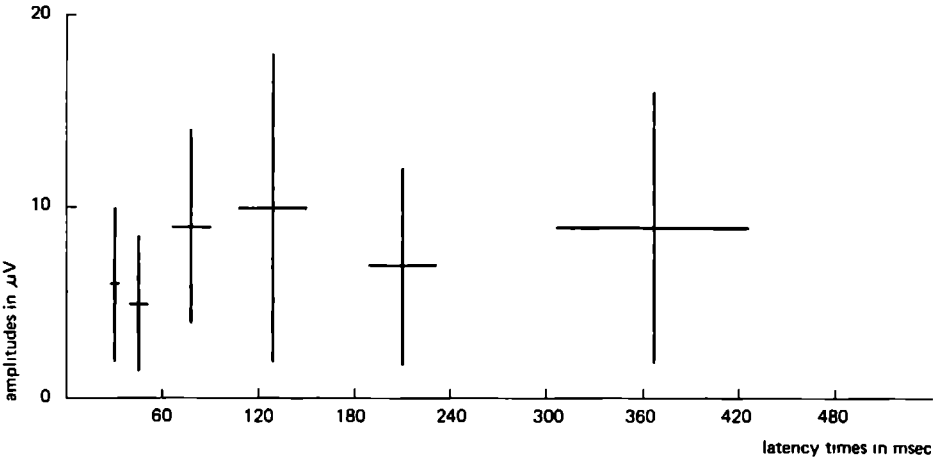

Fig. 3.8. Mean and standard deviations of amplitudes (vertical bars) and latency times (horizontal bars) of peaks present in thalamic intralaminar nuclei after *electrical tooth-pulp* stimulation.

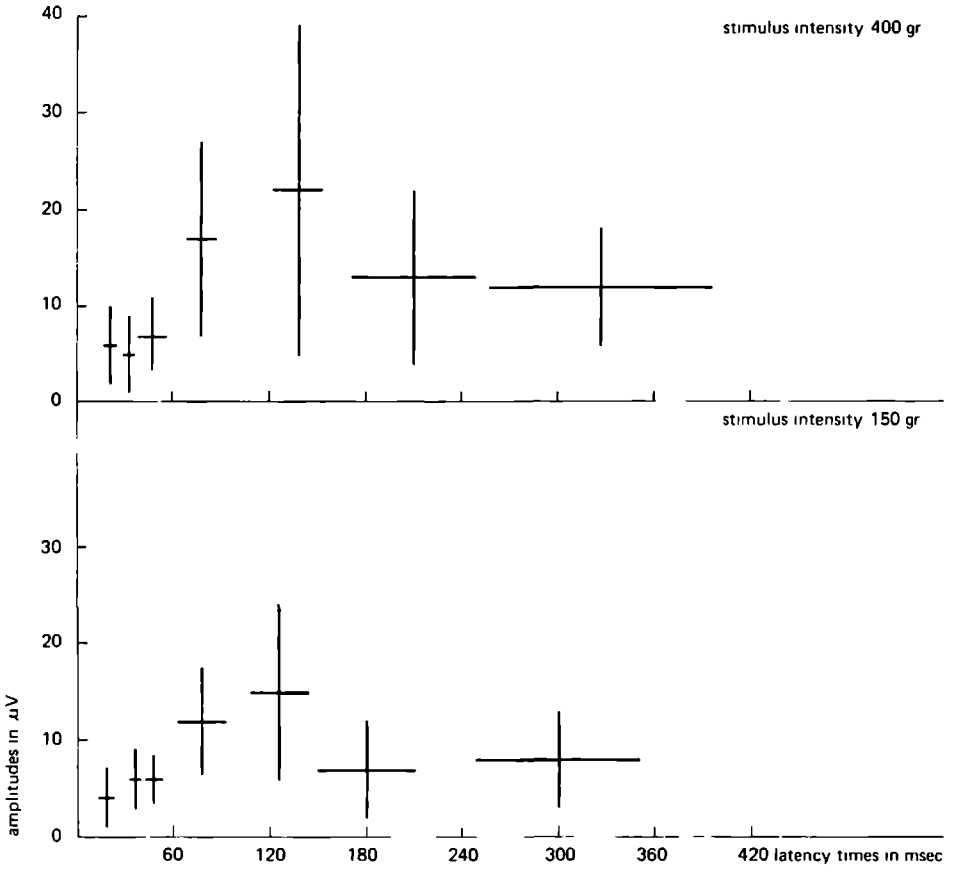

Fig. 3.9. Mean and standard deviations of amplitudes (vertical bars) and latency times (horizontal bars) of the peaks of the *mechanically* evoked potentials in the intralaminar nuclei of the thalamus at two different stimulus intensities.

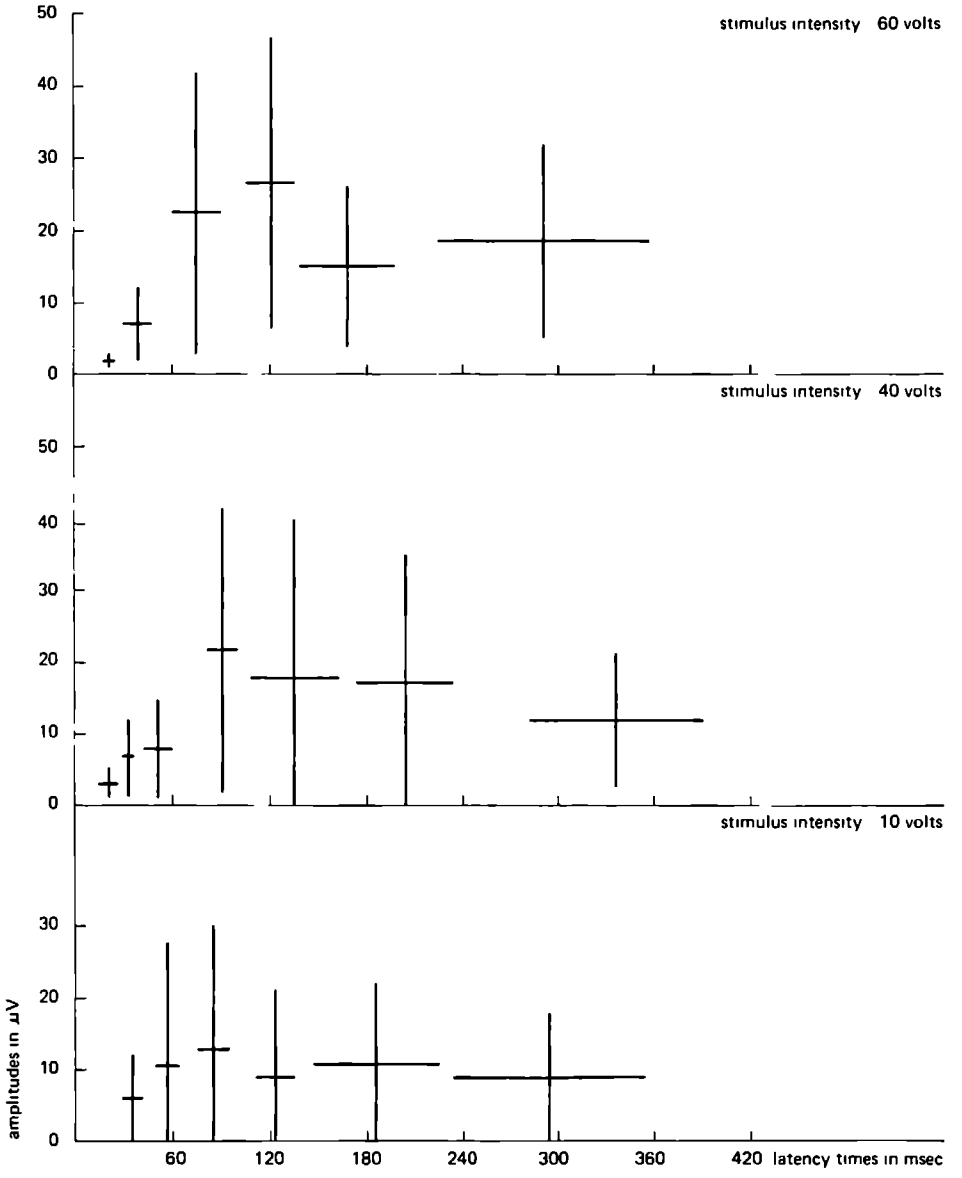

Fig. 3.10. Mean and standard deviations of amplitudes (vertical bars) and latency times (horizontal bars) of the peaks of the *electrically* evoked potentials in the intralaminar nuclei of the thalamus at three different stimulus intensities .

Mechanical stimulation of the hindpaw evoked a thalamic potential with peak latencies of 21, 33, 48, 78, 137, 210 and 327 msec (Fig. 3.9.). The later waves had the largest amplitudes and the greatest stimulus-intensity-dependent amplitudes. Electrical stimulation of the skin of the hindpaw evoked a potential with peak latencies of 20, 33, (48), 76, 119, 165 and 300 msec. The later components increased as the voltage of the stimulus increased and were also the largest components (Fig. 3.10.).

3.3.1.2.3. Discussion and conclusion

The early peaks with latency times of < 50 msec are not always present in the evoked potential as can be seen in the figures 3.8., 3.9., and 3.10. These early components have a small amplitude with all stimulation procedures. The later components have large amplitudes. These peaks show also the largest increase in amplitude as stimulus intensities increase. It seems likely, considering the peak latencies in spinal cord and nucleus reticularis gigantocellularis, that the 76-137 msec peaks are evoked by Aδ fibers, the 165-210 msec peaks by C fibers. The later waves with peak latencies greater than 300 msec are potentials which are generated in the brain itself and probably represent motor responses to the noxious stimulation. With single cell recording of neurons in the centrum medianum - parafascicularis complex ISHIJIMA et al. (1975) demonstrated the existence of two types of neurons, which he called 'A neurons' and 'B neurons'.

'A neurons' have latencies of 30-90 msec and are activated through Aδ fibers, while the 'B neurons' have longer latencies (100-500 msec) and are probably activated by C fiber stimulation. Other workers (ISHIJIMA and SANO 1971; SHIGENAGA et al. 1973) also found a fast and a slow component in the thalamus, these being activated by Aδ and C fibers respectively. This was demonstrated by selective blocking of the myelinated Aδ fibers (CHUNG et al. 1979). All these authors agree that the CM-parafascicularis complex receives impulses from large receptive somatic areas and that a diffuse burning pain is felt after stimulation in this area.

It can be concluded that in those experiments both A (Aδ) and B (C fiber) neurons are stimulated and that noxious stimuli have reached the thalamus, especially when high intensities of stimulation are used.

3.3.1.3. The hypothalamus

3.3.1.3.1. Introduction

The most important integration centers of sympatic, parasympatic and hormonal balance lie in the hypothalamus. The lateral parts of this brain center receive nociceptive input (BOWSHER 1975). The hypothalamus is involved in the autonomic and hormonal reactions to the affective emotional reflexes following pain perception. In rats a lowering of the jump and flinch threshold is seen after destruction of this part of the hypothalamus, indicating a state of hyperalgesia. The hypothalamus has pain-modulating and analgesia-inducing functions (HARVEY and LINTS 1971). It seemed worth while to investigate the nociceptive mechanically and electrically evoked potentials in this brain structure in dogs.

Neuroadenolysis of the pituitary gland is a method of relieving intractable cancer pain (MORICCA 1974).

3.3.1.3.2. Results

Nociceptive tooth-pulp stimulation evoked a potential in the anterior hypothalamus which was characterized by peaks with mean latencies of 24, 42, 66, 106, 178 and 291 msec (Fig. 3.11.). The later peaks had larger amplitudes than the first ones.

Mechanical stimulation of the hind paw evoked a hypothalamic potential with peak latencies of 35, 57, 90, 150, 245 and 380 msec (Fig. 3.12.).

The largest components (> 50 msec) had the largest amplitudes, which increased as the intensity of the stimuli increased.

Electrical stimulation of the hind paw evoked a thalamic potential with mean peak latencies of 20, 33, 46, 67, 88, 120, 203 and 372 msec (Fig. 3.13.). The amplitudes of the later peaks (i.e. > 50 msec) were larger than those of the early components, and they also increased the most as the stimulus intensity increased.

3.3.1.3.3. Discussion and conclusion

In the hypothalamus also, the three methods of stimulation evoked at least six waves. In the electrically evoked potential an extra peak with a mean latency of 93 msec is present. The other waves of the potentials evoked by the three different stimulation methods are in agreement in

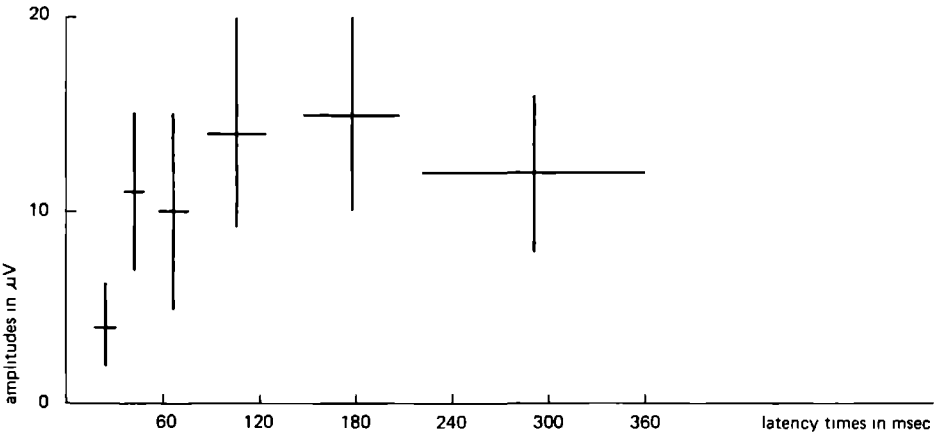

Fig. 3.11. Mean and standard deviations of amplitudes (vertical bars) and latency times (horizontal bars) of the peaks in the hypothalamus after *electrical tooth-pulp* stimulation.

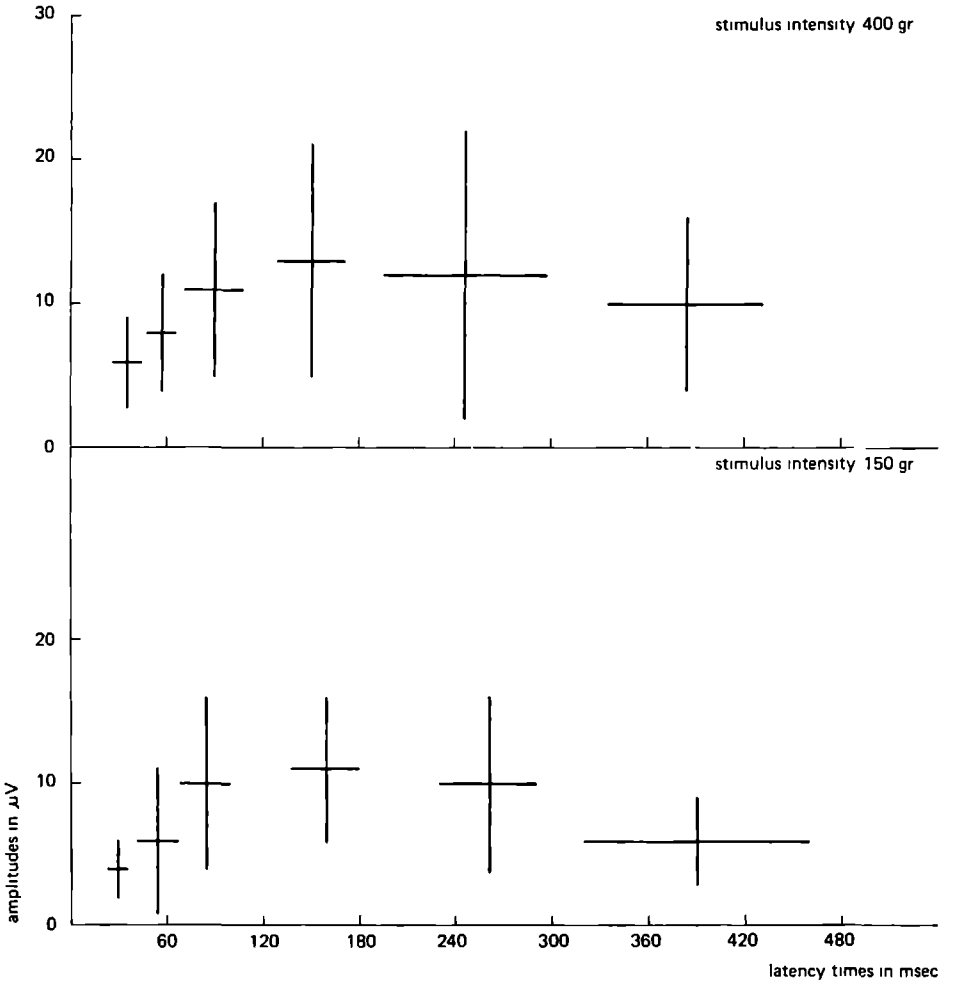

Fig. 3.12. Mean and standards deviations of amplitudes (vertical bars) and latency times (horizontal bars) of the peaks in *mechanically* evoked potentials in hypothalamus at two different stimulus intensities.

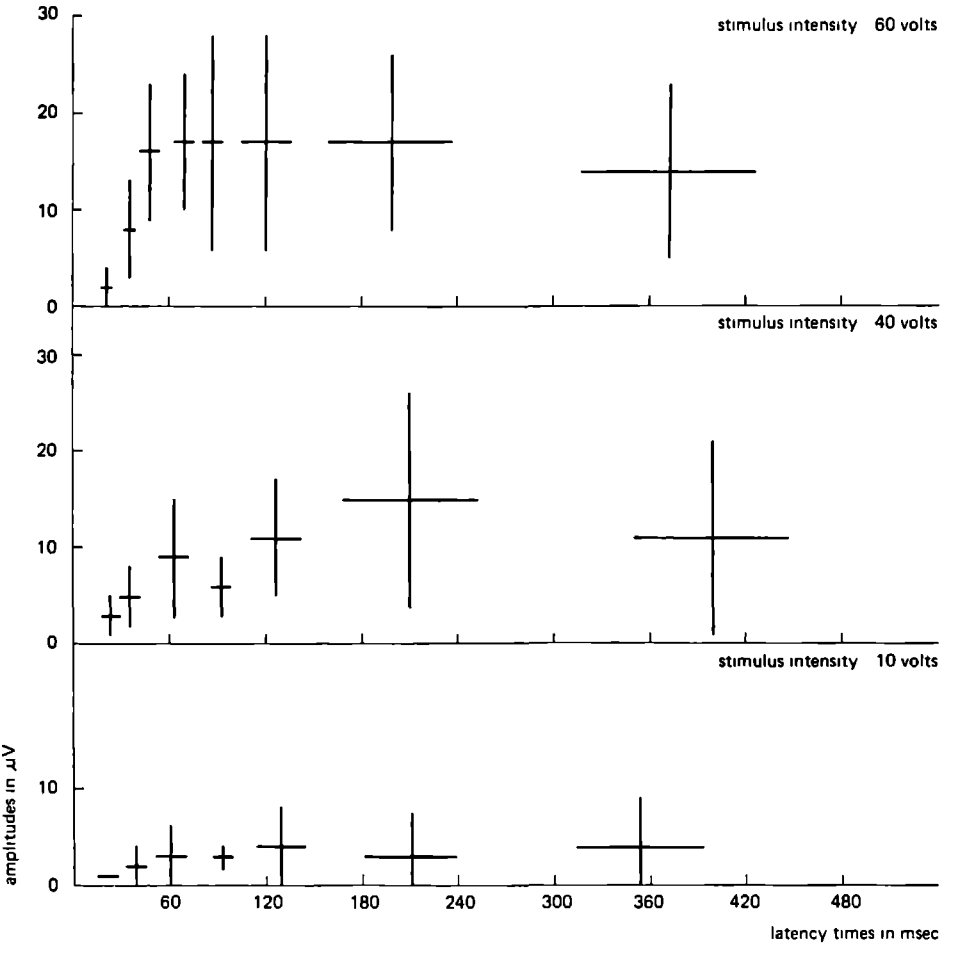

Fig. 3.13. Mean and standard deviations of amplitudes (vertical bars) and latency times (horizontal bars) of the peaks in *electrically* evoked potentials in the hypothalamus at three different stimulus intensities.

latency times.

Small differences in peak latency times are also present here. If the differences in conduction velocity of the peripheral fibers are taken into account the following conclusion can be drawn. The peaks with latencies smaller than 70 msec are probably related to Aβ or very fast conducting Aγ fibers. The peaks with latencies of 70-158 msec are Aδ fiber-evoked peaks. The next one, 178 with tooth-pulp, 245 with mechanical and 203 with electrical stimulation, is a C fiber response. The later responses are again postsynaptic cerebral continuing patterns or motor responses.

The above results are in agreement with those found in rats by SHIGENAGA et al. (1973). Two peaks with latencies of 20-30 and 40-90 msec are described by these authors. If the size of the animal is taken into account, the distance covered by an impulse in the peripheral nerve of a dog is 3-4 times as long as in a rat. If this factor is used to multiply the latency times in rats a high degree of agreement exists with the latency times found in our dogs. In monkeys and rabbits a 30 msec peak was also detected after tooth-pulp stimulation (TROUWBORST 1982).

Tooth-pulp, mechanical and *electrical stimulation* evoke potentials in the hypothalamus mediated by Aδ and C fibers. Nociceptive stimulation evokes, in dog's hypothalamus, large potentials, increasing as stimulus intensity increases. Thus the hypothalamus plays a role in conduction of noxious impulses.

3.3.1.4. Amygdala complex

3.3.1.4.1. Introduction

The amygdala, as a part of the limbic system, is responsible for affective and emotional behavior (HEATH et al. 1974).

It receives input from regions which are mentioned in Chapter 1 as playing a role in nociception, such as the nucleus parafascicularis, the nucleus paraventricularis and the nucleus centralis thalami, but also from lateral and ventromedial parts of the hypothalamus (MEHLER 1980). LICO et al. (1974) used guineapigs for study of the influence of some limbic structures upon somatic and autonomic manifestations of pain. Defensive and offensive movements and high frequency vocalizations were indicative of pain perception after *tooth-pulp stimulation. Electrical stimulation* of certain

parts of the limbic structure inhibited these manifestation while that of other parts increased them. This points to an involvement of limbic structures in pain perception.

We wished to ascertain whether in dogs the amygdala is also involved in nociceptive evoked potentials.

3.3.1.4.2. Results

Electrical tooth-pulp stimulation evoked in the left amygdala a potential with mean peak latencies of 19, 47, 77, 117, 183, 274 and 376 msec (Fig.3.14.). The later peaks were present in all animals and were the largest in amplitude.

Mechanical hindpaw-skin stimulation evoked in this brain region a potential with peak latencies of 35, 79, 169, 278 and 406 msec(Fig.3.15.). The later components were the largest in amplitude.

Electrical skin stimulation evoked a potential with mean peak latencies of 33, 74, 120, 181 and 324 msec (Fig. 3.16.). The amplitudes of the later components increased the most in amplitudes as the intensity of the stimulus increased.

3.3.1.4.3. Discussion and conclusion

As in recordings of the evoked potentials in the other brain structures, the early peaks (< 50 msec) seem to be induced by Aβ and Aγ fibers, the 74-169 msec peak by Aδ and the 181-278 msec peaks by C fiber stimulation. The later ones are probably postsynaptic circulating cerebral electrical patterns as a reaction to noxious stimulation. They might also represent the motor response of the higher brain centers. In the amygdala also the later components (> 50 msec) increase as the intensity of the *mechanical* or *electrical stimulation* increases, and the early components are not always present. Unfortunately we have been unable to find any studies on nociceptive evoked amygdala potentials either in man or in other mammals.

From our own experiments it is obvious that those stimuli which activate Aδ and C fibers give high-amplitude potentials in the amygdala and that these waves increase greatly as the intensity of the stimulus increases. It is probable that the amygdala plays a role in conduction of noxious stimuli.

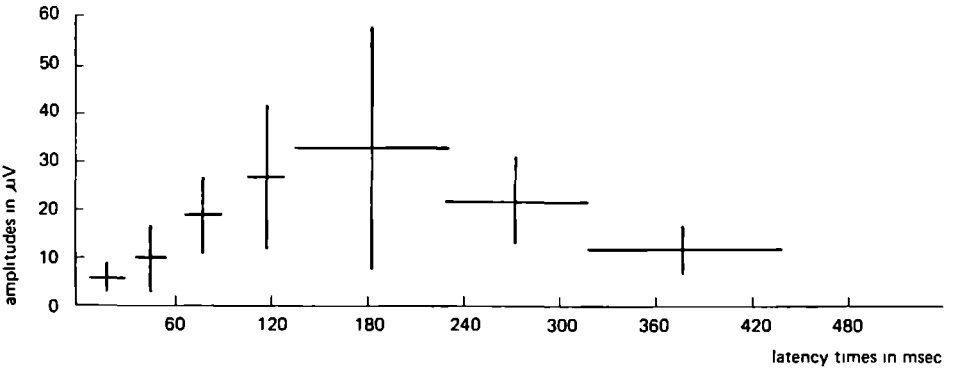

Fig. 3.14. Mean and standard deviations of amplitudes (vertical bars) and latency times (horizontal bars) of the peaks in the contralateral amygdala after *electrical tooth-pulp* stimulation.

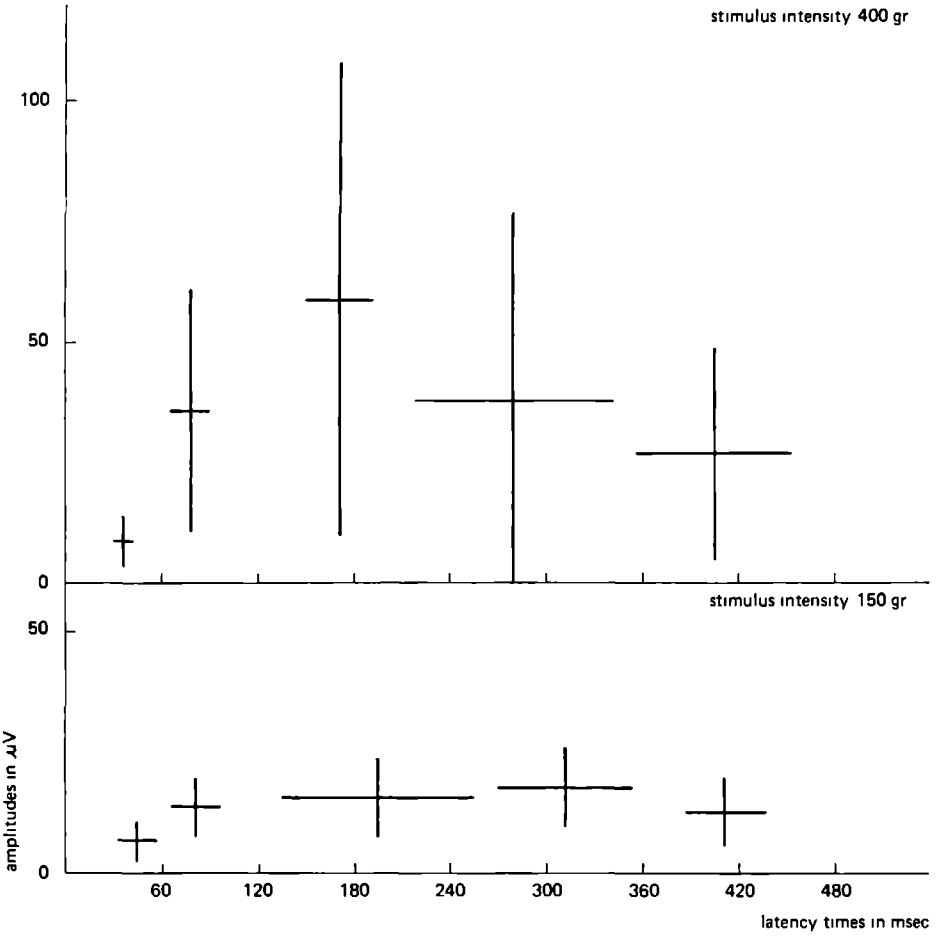

Fig. 3.15. Mean and standard deviations of amplitudes (vertical bars) and latency times (horizontal bars) of the peaks in *mechanically* evoked potentials in the contralateral amygdala at two different stimulus intensities.

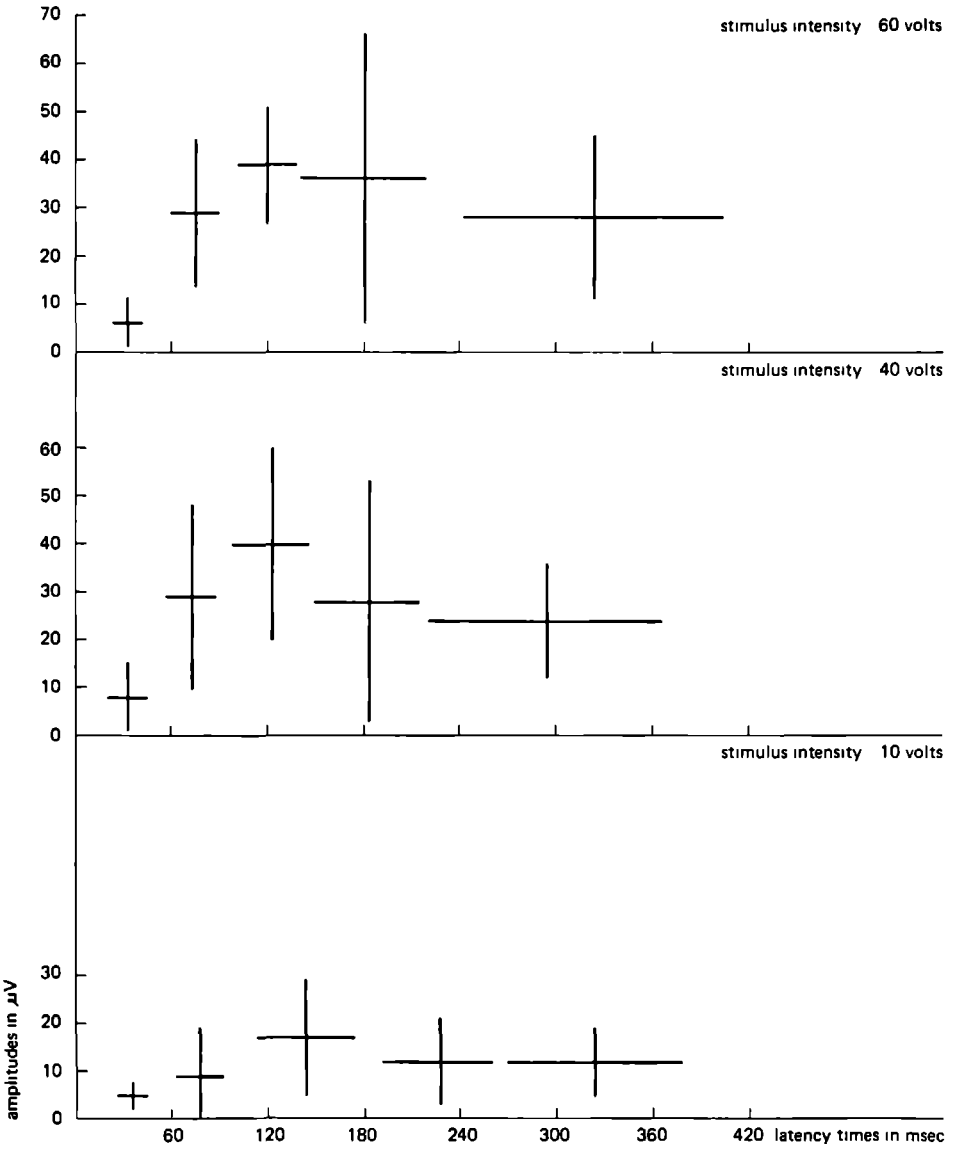

Fig. 3.16. Mean and standard deviations of amplitudes (vertical bars) and latency times (horizontal bars) of the peaks in *electrically* evoked potentials in the contralateral amygdala at three different stimulus intensities.

3.3.2. Cerebral cortex

3.3.2.1. Introduction

The somatosensory cortex is divided into two parts: areas S I and S II (POWELL 1977). S I lies in the posterior sigmoid and coronal gyrus and extends in the dog for about 4 mm into the medial wall of the hemisphere caudal to the crucial sulcus. The lateral limit is the anterior suprasylvian sulcus. In man it is called the area Rolandi. S II is situated just lateral and caudal to S I. The caudal limit is at the level of the junction of the ansate, lateral and coronal sulci (HAMUY et al. 1956). S I receives input from ventroposterior thalamus, intralaminar nuclei, and nucleus centralis lateralis. The contralateral side of the body is somatotopically represented.

S II receives input also from ventroposterior nuclei of the thalamus. There are branches which also go to S I. The intralaminar parts of the thalamus also project to this region. Both sides, i.e. left and right, react almost identically to stimulation of the body (POWELL 1977; MIYAKAWA and KUSAMA 1979).

The afferent and efferent connections of this part of the cortex and its function have been mainly investigated in cats.

In cats, after destruction of the sensory cortex I and II an ipsilateral degeneration of the motor cortex (area 4) developed; part of area 6 and part of the parietal region (area 5) and contralaterally S I and S II also showed degenerative aspects. In the thalamus the nucleus ventralis posterior and the posterior nuclear group were affected (NATHAN 1977). Bilateral extirpation of S II led in cats to a decrease in flight response after electrical foot shock; S I extirpation bilaterally was less effective. Bilaterally both S I and S II extirpation not only raised the flight threshold but also increased latency time before the animal responded to foot shock. This effect was still more pronounced if the surrounding parts of S II were also extirpated (BERKLEY and PARMER 1974).

Spinal laminectomy at T2 in cats induced paraplegia and resulted in an absence of evoked potentials in the sensory cortex after fore-paw stimulation (SINGER et al. 1977-1978).

In dogs, the early evoked potentials were also abolished by transection of the dorsal column of the spinal cord and the dorsal part of the lateral

funiculus of the spinal cord. The later components however, remained (SINGER et al. 1977-1978).

The late components of the evoked potential are a reflection of the information content of the stimulus (SUTTON et al. 1967). The importance of the cortical evoked potentials in dogs in relation to nociception will be presented in the following paragraph.

3.3.2.2. The SEP in the contralateral somatosensory cortex I and II

3.3.2.2.1. Results

Tooth-pulp stimulation

Fig. 3.17. shows the mean and standard deviations of both amplitudes and latency times of the peaks in the somatosensory cortex areas I and II after tooth pulp stimulation. The latency times in the S II cortex were shorter than in the S I cortex. In both regions a response with six peaks was found. The mean latencies were 27 (S II), 30-38, 52-56, 75-72, 98-109, 145-199, and two late waves in S I 228 and 376 msec. The amplitudes in S II were greater than those in S I. The early components were not always present and the very late component was seen in S I (376 msec) in only 50% of the experiments. The later potentials > 50 msec, were larger in amplitude than the early ones.

Mechanical stimulation

Mechanical stimulation to the right hind leg evoked peaks in the contralateral sensory cortex I with latencies of 21, 29, 38, 52, 121 and 210 msec (Fig. 3.18. above); in the contralateral sensory cortex II with latencies of 21, 37, 60, 111, 163 and 250 msec (Fig. 3.18. below).

Fig. 3.19. shows the mean and latencies of the peaks found in the combined S I/II leads after mechanical stimulation. The mean latencies were comparable with those for the S I and S II leads separately, i.e. 16, 25, 30, 62, 132 and 234 msec. The latencies of the peaks in the S II potential were greater than those in the S I potential, while the latencies in S I/II were intermediate.

In the sensory cortex II, a peak with a latency of approximately 160 msec was present which was not found in the S I and S I/II evoked potentials. Very large amplitudes were found at latencies of more than 50 msec in the contralateral sensory cortex I and II. The early components were not

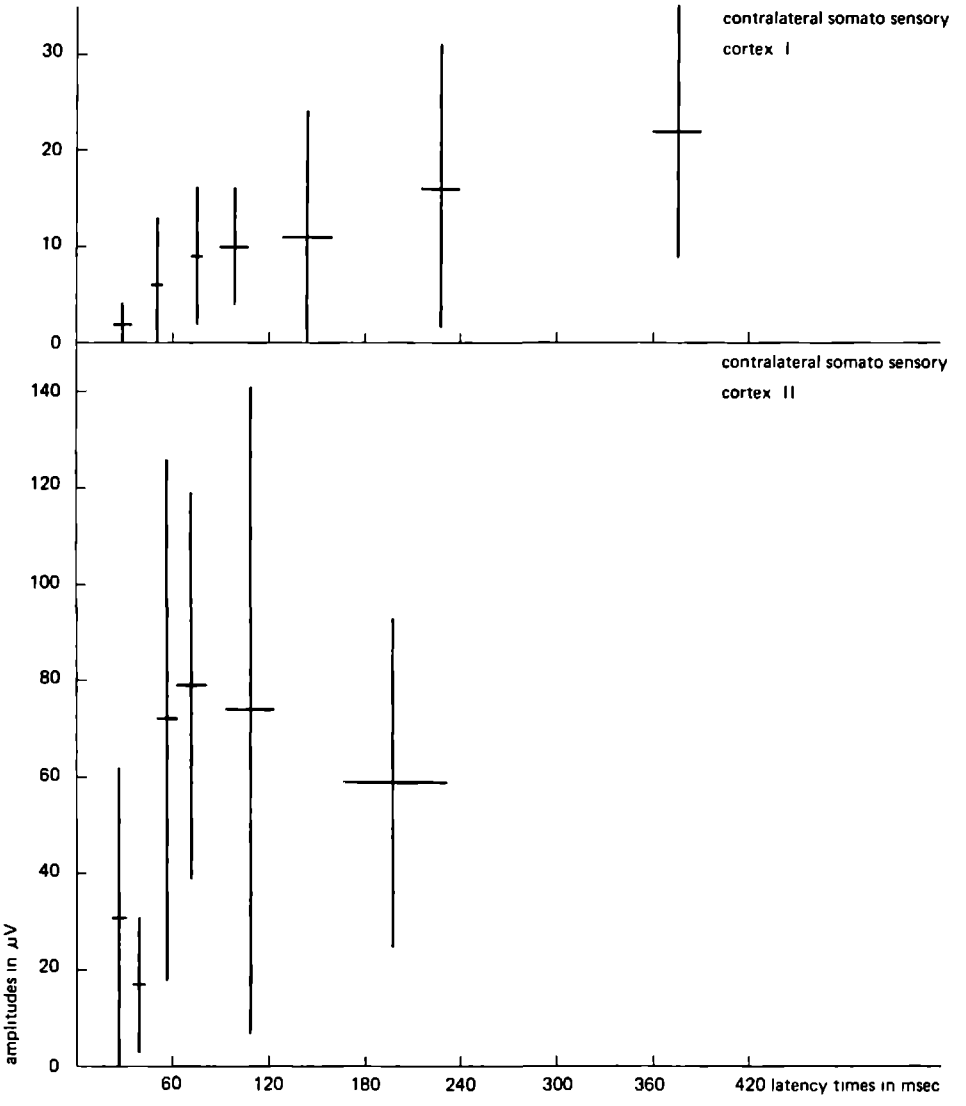

Fig. 3.17. Mean and standard deviations of amplitudes (vertical bars) and latency times (horizontal bars) of the peaks in contralateral somatosensory cortex I (upper figure) and contralateral somatosensory cortex II (lower figure) after *electrical tooth-pulp* stimulation.

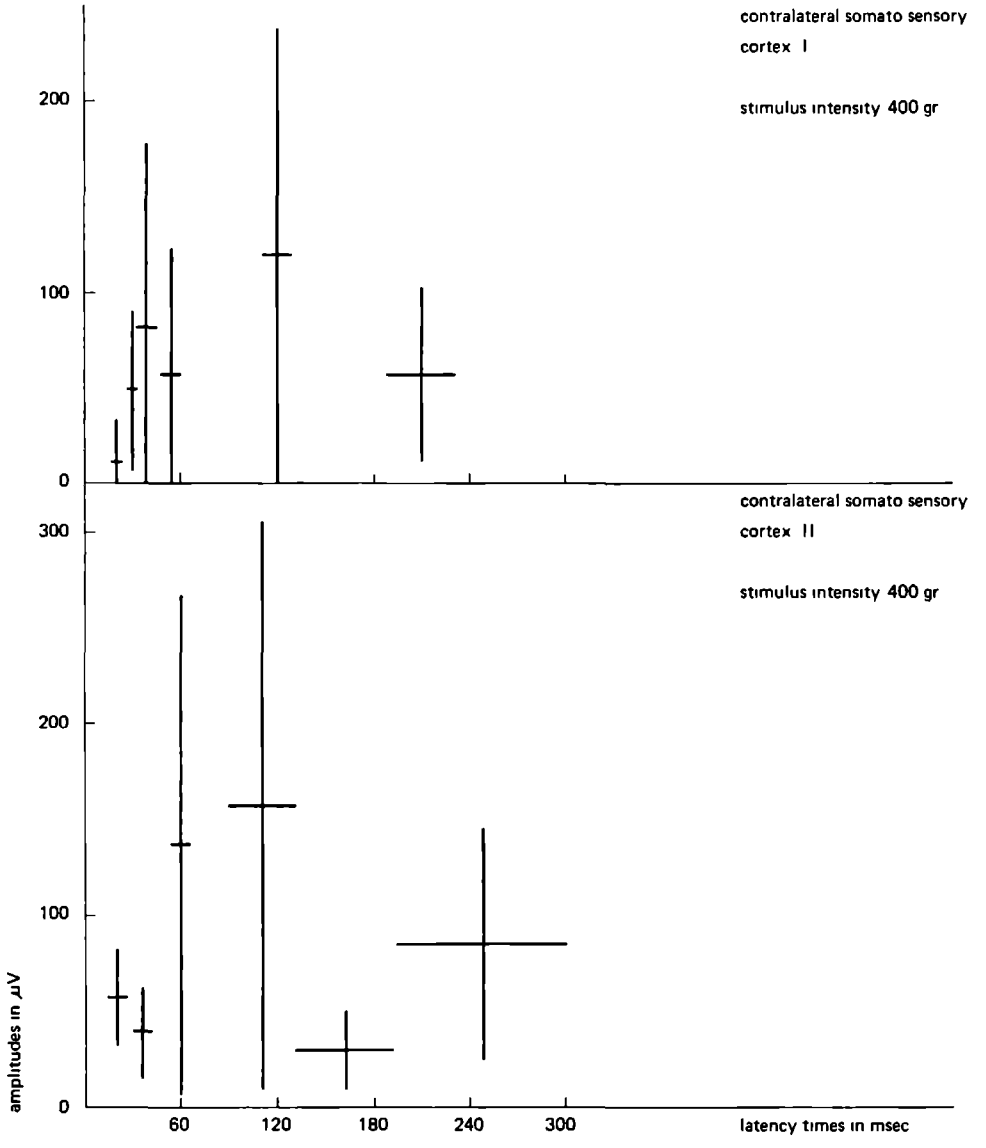

Fig. 3.18. Mean and standard deviations of amplitudes (vertical bars) and latency times (horizontal bars) of the peaks in *mechanically* evoked potentials in the contralateral somatosensory cortex I (above) and the contralateral somatosensory cortex II (below).

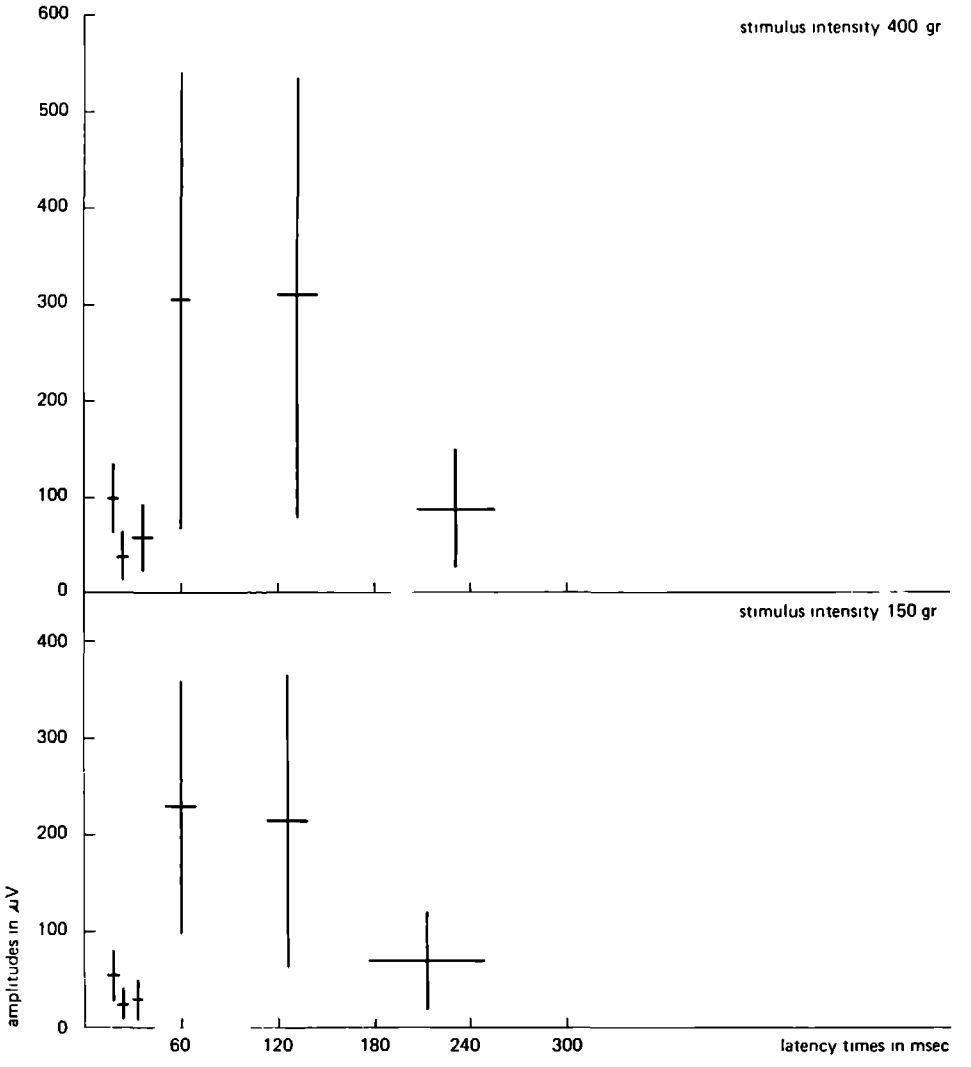

Fig. 3.19. Mean and standard deviations of amplitudes (vertical bars) and latency times (horizontal bars) of the peaks in *mechanically* evoked potentials in the combined contralateral somatosensory cortex I and II lead at two different stimulus intensities.

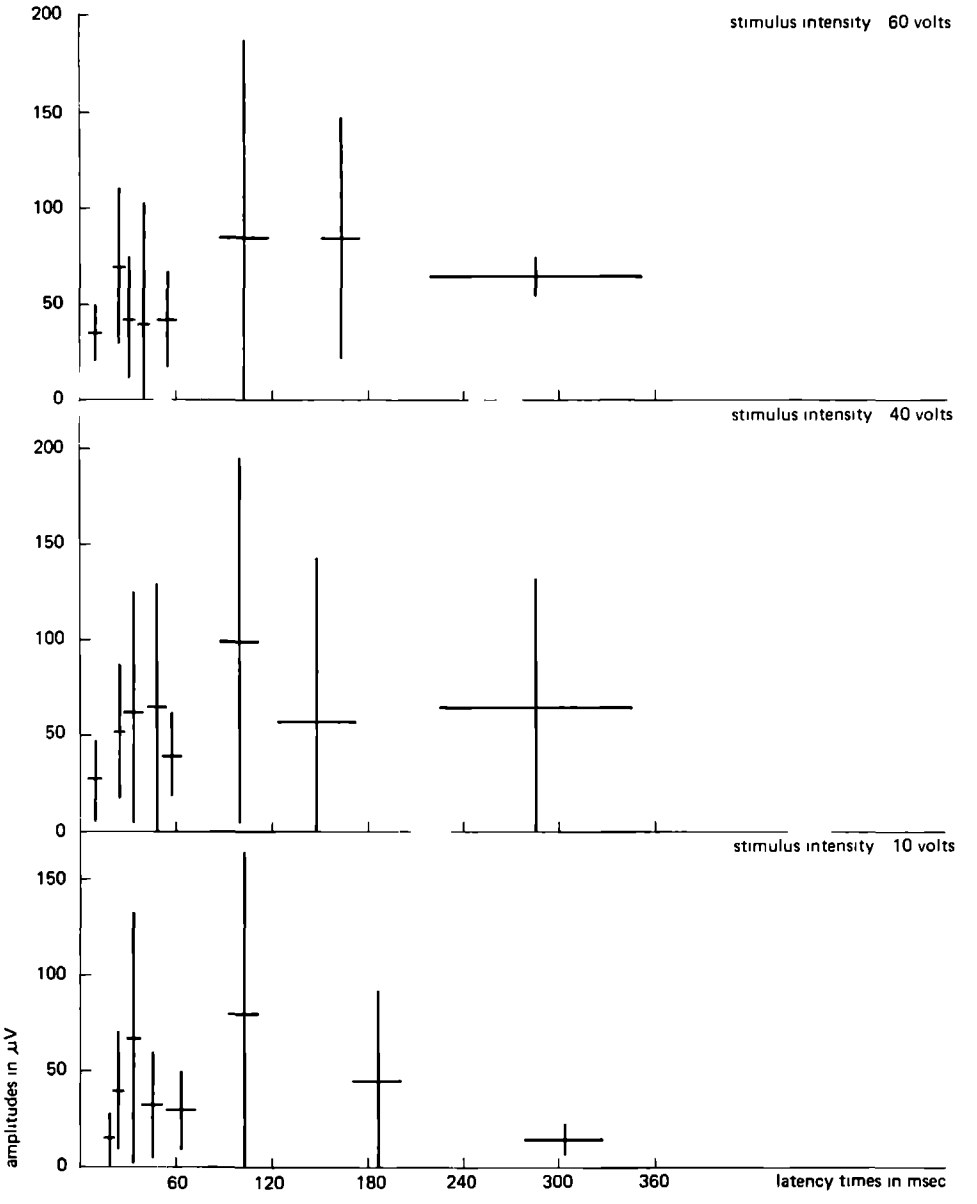

Fig. 3.20. Mean and standard deviations of amplitudes (vertical bars) and latency times (horizontal bars) of the peaks in *electrically* evoked potentials in the contralateral somatosensory cortex I at three different stimulus intensities.

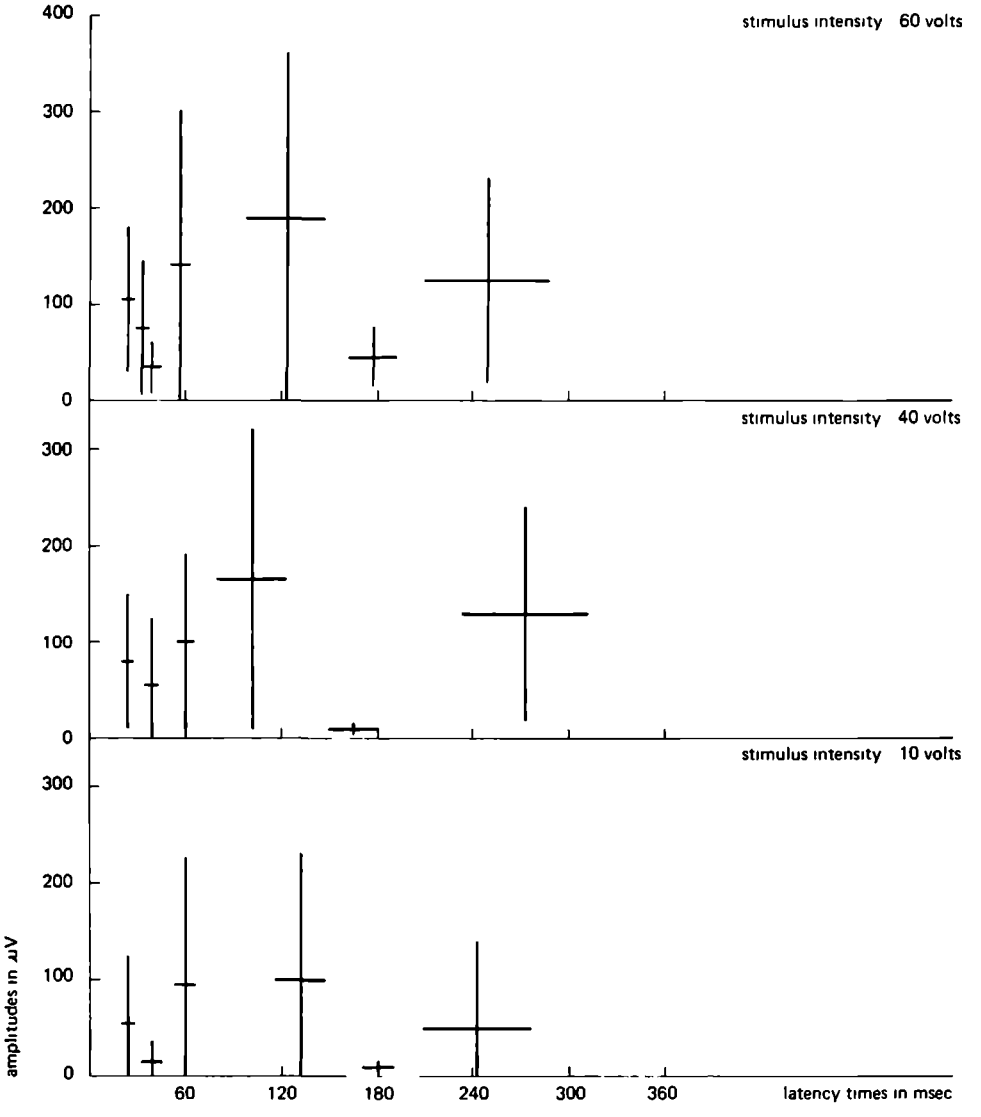

Fig. 3.21. Mean and standard deviations of amplitudes (vertical bars) and latency times (horizontal bars) of the peaks in *electrically* evoked potentials in the contralateral somatosensory cortex II at three different stimulus intensities.

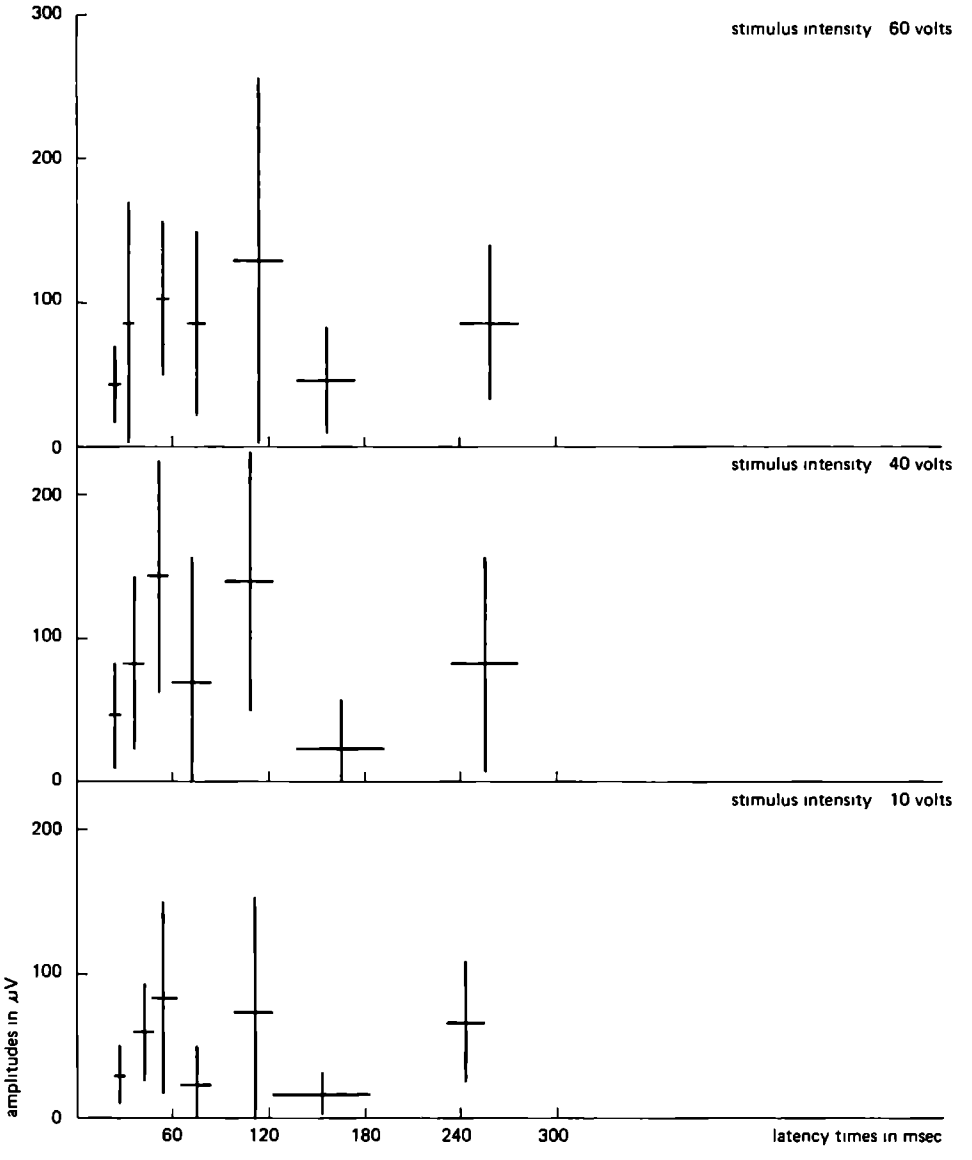

Fig. 3.22. Mean and standard deviations of amplitudes (vertical bars) and latency times (horizontal bars) of the peaks in *electrically* evoked potentials in the combined contralateral somatosensory cortex I and II lead at three different stimulus intensities.

always present.

Electrical stimulation

In Figs.3.20, 3.21., 3.22, the evoked potential of electrical stimulation of the hind paw is shown. Here 7-8 peaks were seen. In S I a double peak with a latency of 30 and 40 msec was present. For the early components (< 100 msec), the latencies found in the combined S I/II lead were much longer than those in the S I and S II leads separately. For the components above 100 msec no differences were seen. Again, very large amplitudes were found in the later components. The components with a latency of 170 msec was not always present.

3.3.2.2.2. Discussion and conclusion

Comparison of the three stimulus methods gives the following results.

Tooth pulp stimulation evokes peaks with shorter latency in S II than in S I. For *electrical* and *mechanical hind-paw stimulation* the opposite is seen. The amplitudes seen in mechanical, electrical and tooth-pulp evoked potentials are all of the same magnitude in the S II area but not in the S I area. In the latter area, tooth-pulp evoked potentials are very small in amplitude compared with mechanically and electrically evoked potentials. These findings can be explained by the somatotopic organization of S I. The electrodes in this area are placed in the hind paw region. The region where the mouth and tooth are represented lies more laterally, next to the S II area. Thus, for *hind-paw stimulation* the correct region in S I is used, but this is not the case for *tooth-pulp stimulation.*

In man, *electrical tooth-pulp stimulation* evokes a potential in the sensory cortex I with peak latencies of 60-80, 80-140, 170-260 and 320-400 msec (ROHDEWALD et al. 1980). These results are comparable with ours, except that in our material two early peaks and one with a latency of 145 msec are present.

CHATRIAN et al. (1975) found in human subjects an electrically evoked tooth-pulp potential in S I with latencies of 38,72, 134, 234 and 315 msec and in S II with latencies of 74 and 108 msec. In our dogs an early component (52 msec) and a late component (145 msec) in S I and 3 early components (27, 38 and 56 msec) and one late component (199 msec) in S II were found in addition to these.

In rabbits and primates a tooth-pulp evoked potential of 20 and 30 msec was found (TROUWBORST 1982).

In clinically normal dogs a response in S I after *electrical percutaneous stimulation* of the sciatic nerve was found with latencies of 14, 20 and 44 msec. A few late peaks have been mentioned but not further defined (KORNEGAY et al. 1981). In cats under pentobarbital anesthesia, selective activation of Aα fibers evoked a peak with a latency of 19-29 msec and selective Aδ fiber stimulation a peak with a latency of 40-60 msec. Unfortunately no C fiber response has been found, but it would have a longer latency than 60 msec (ALPSAN 1981). In man, *transcutaneous electrical stimulation* evokes peaks in S I with latencies of 19 and 29 msec (SCHNEIDER 1981), 25-27 and 36 msec (CHATRIAN et al. 1975); 23, 31, 40, 49, 64, 87, 114 and 147 msec (YAMAUCHI et al. 1981); 13-18, 16-22, 21-28, 30-37, 38-50. 48-65 and 62-102 msec (KÜHN et al. 1973).

Mechanical noxious or *thermal* noxious *stimuli* evoke in human sensory cortex I peaks with latencies of 130-160 and 230-300 msec (CARMON et al. 1976)

The peak latency times found in this study and by other workers are in agreement, except that the number of potentials found may be different. It is probable that some potentials are so small in amplitude that they are not discerned in all studies.

Tooth-pulp, needle-prick and *electrical stimuli* evoke in the contralateral cortex, both I and II, potentials which are probably mediated by Aβ , Aγ , Aδ and C fibers. The early peaks (latencies < 50 msec) are Aβ and Aγ evoked peaks. The peaks with latencies between 50 and 150 msec are evoked by Aδ fibers and the peaks with latencies of 150-250 msec by C fibers. The peaks with latencies greater than 50 msec are those which increase the most in amplitude. It seems likely that these later waves are highly involved in nociception.

3.3.2.3. The SEP in ipsilateral somatosensory cortex I and II

3.3.2.3.1. Results

Tooth-pulp stimulation

Potentials evoked by *electrical tooth-pulp stimulation* in the ipsilateral sensory cortex I had peak latencies of 30, 59, 79, 116 and 247 msec (Fig. 3.23 above). In S II these latencies were 34, 58, 141 and 320 msec (Fig. 3.23 below).

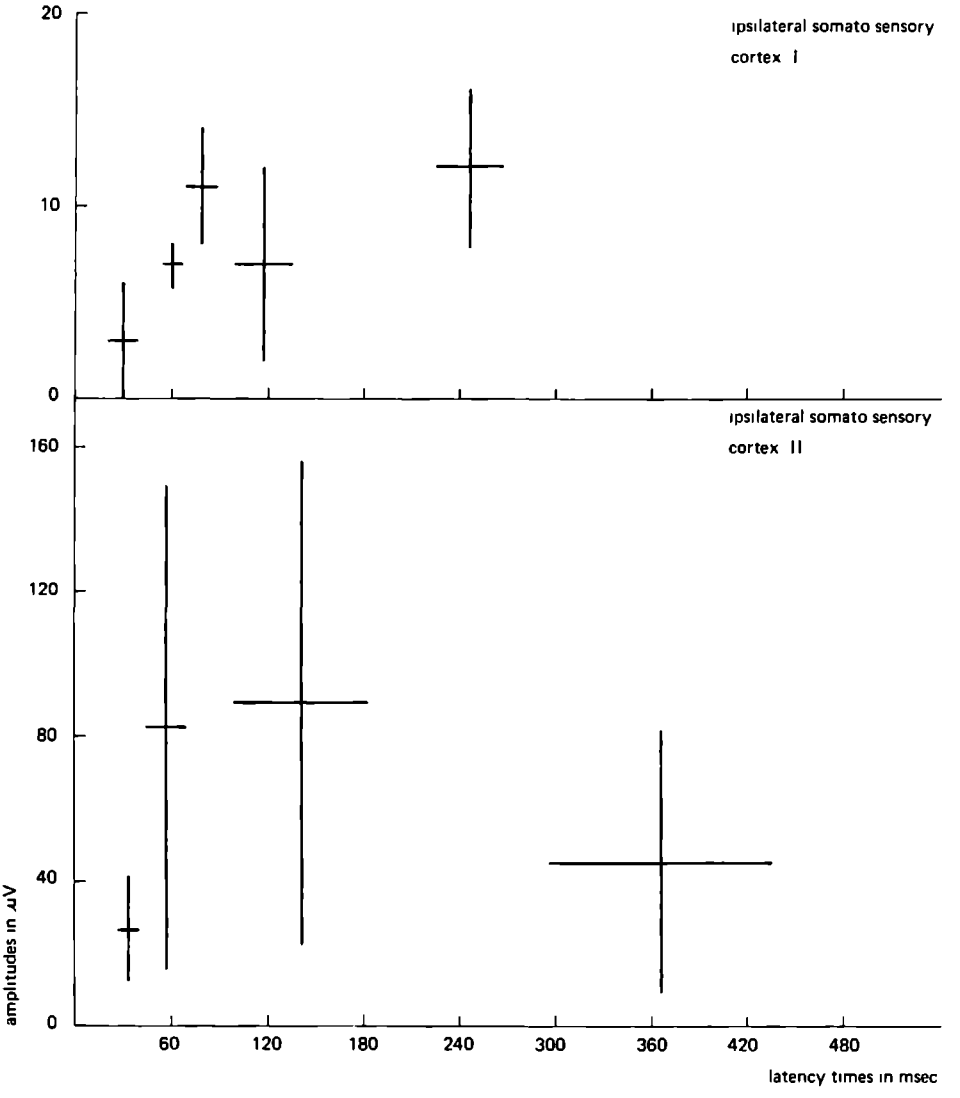

Fig. 3.23. Mean and standard deviations of amplitudes (vertical bars) and latency times (horizontal bars) of the peaks in the ipsilateral somatosensory cortex I (above) and in the ipsilateral somatosensory cortex II (below) after *electrical tooth-pulp* stimulation.

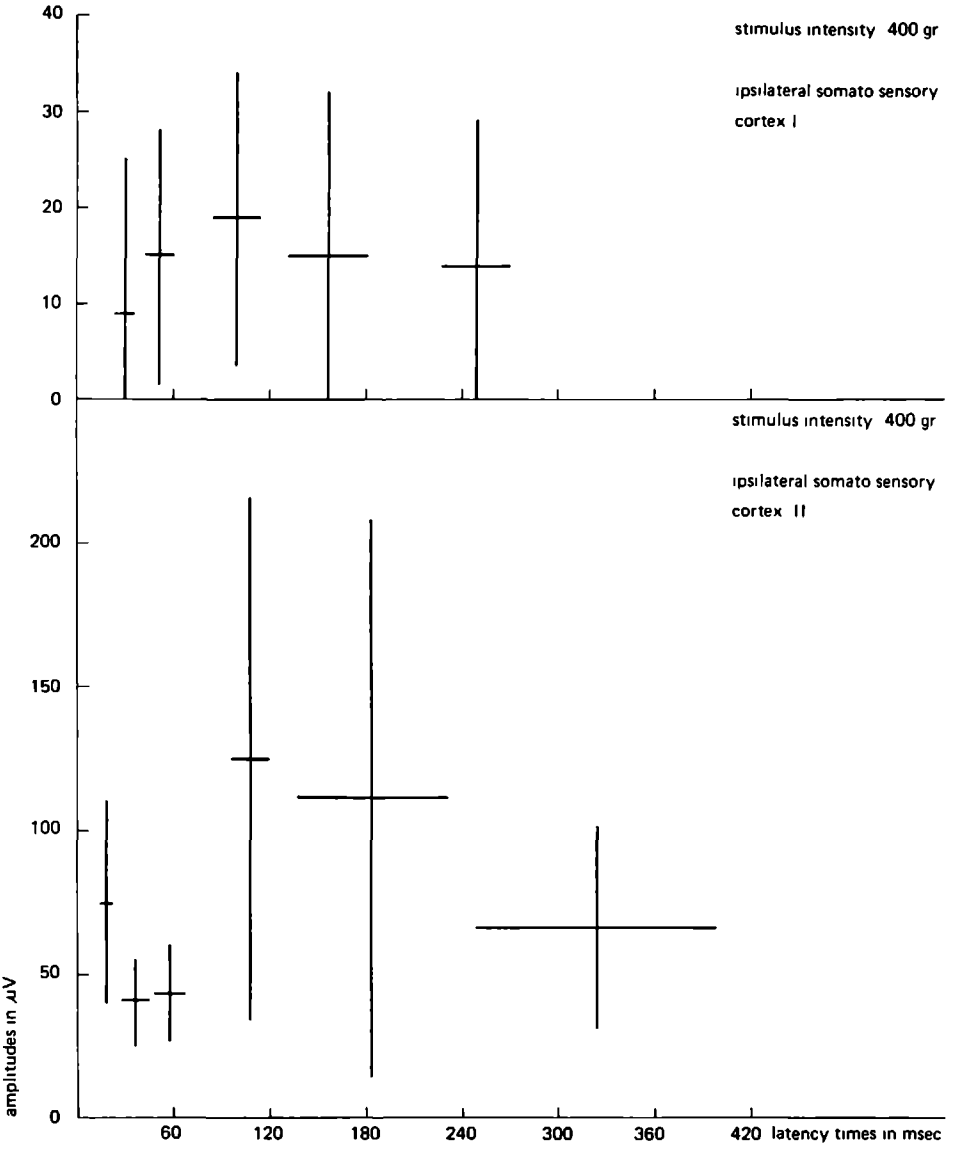

Fig. 3.24. Mean and standard deviations of amplitudes (vertical bars) and latency times (horizontal bars) of the peaks in *mechanically* evoked potentials in the ipsilateral somatosensory cortex I (above) and the ipsilateral somatosensory cortex II (below).

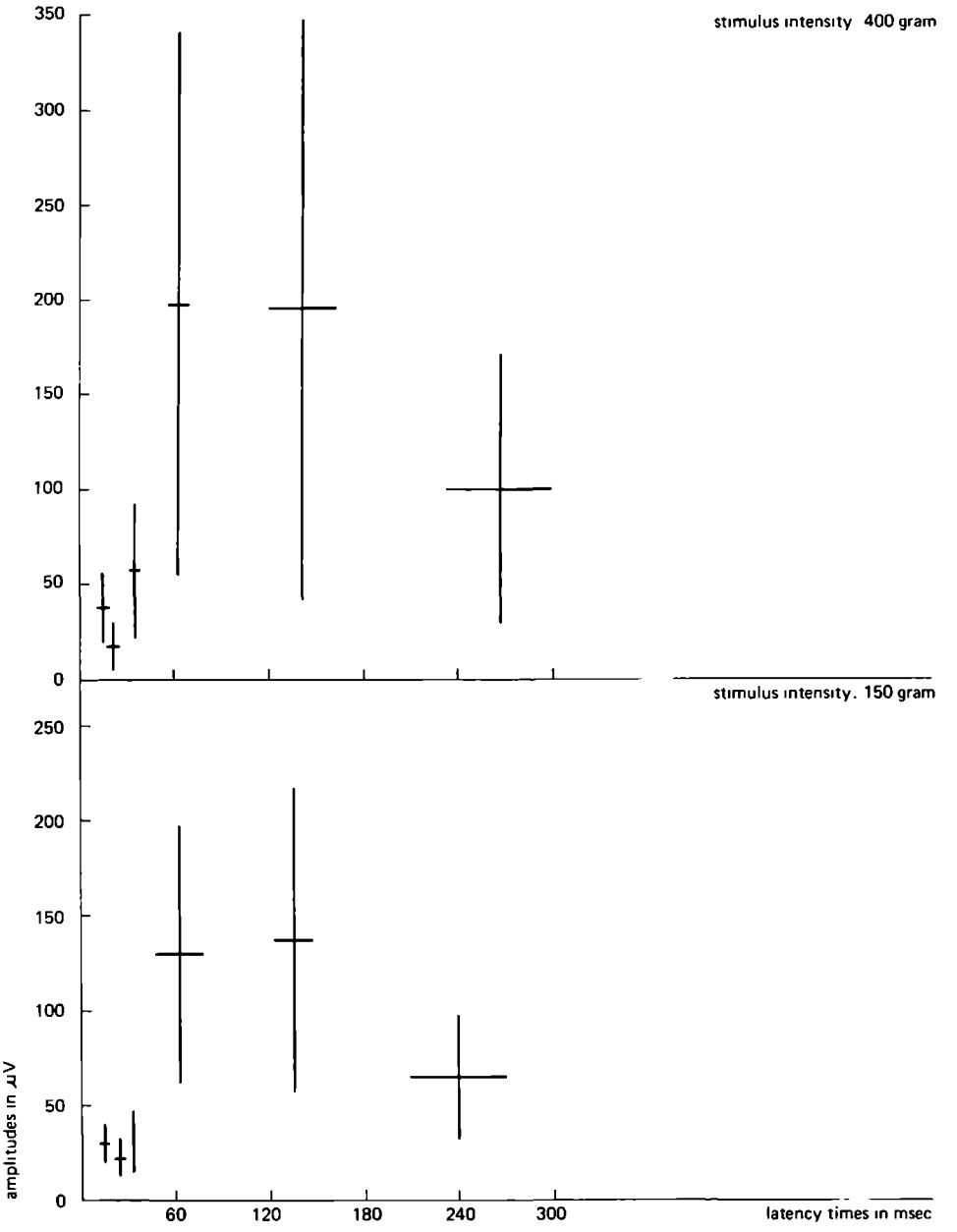

Fig. 3.25. Mean and standard deviations of amplitudes (vertical bars) and latency times (horizontal bars) of the peaks in *mechanically* evoked potentials in the combined ipsilateral somatosensory cortex I and II lead at two different stimulus intensities.

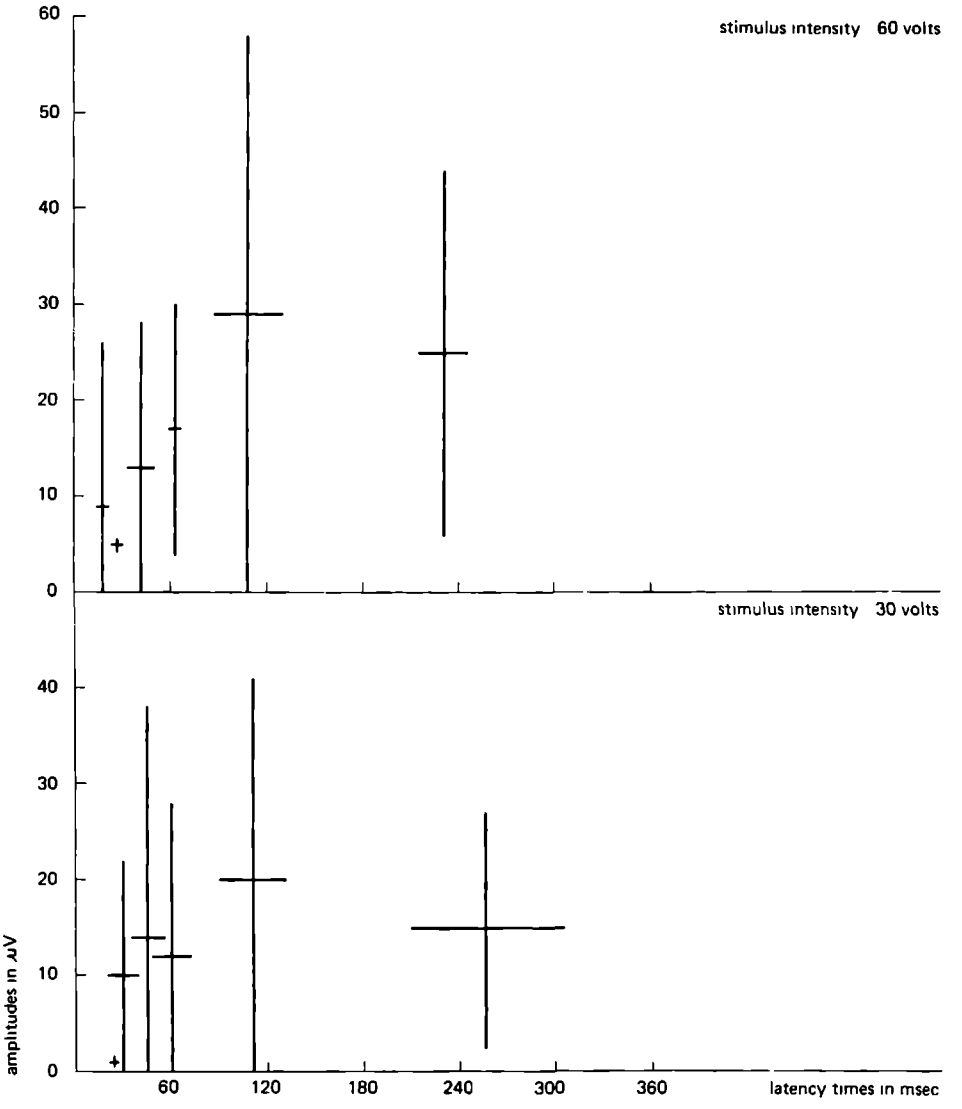

Fig. 3.26. Mean and standard deviations of amplitudes (vertical bars) and latency times (horizontal bars) of the peaks in *electrically* evoked potentials in the ipsilateral somatosensory cortex I at two different stimulus intensities.

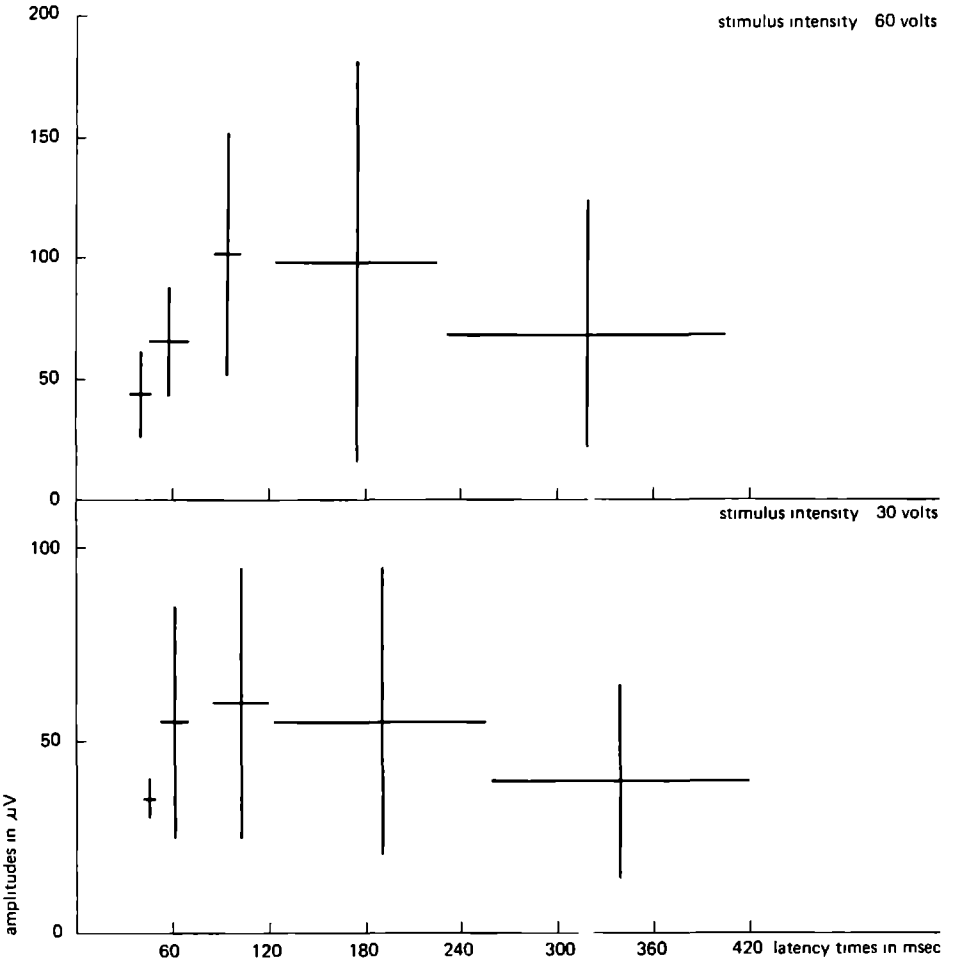

Fig. 3.27. Mean and standard deviations of amplitudes (vertical bars) and latency times (horizontal bars) of the peaks in *electrically* evoked potentials in the ipsilateral somatosensory cortex II at two different stimulus intensities.

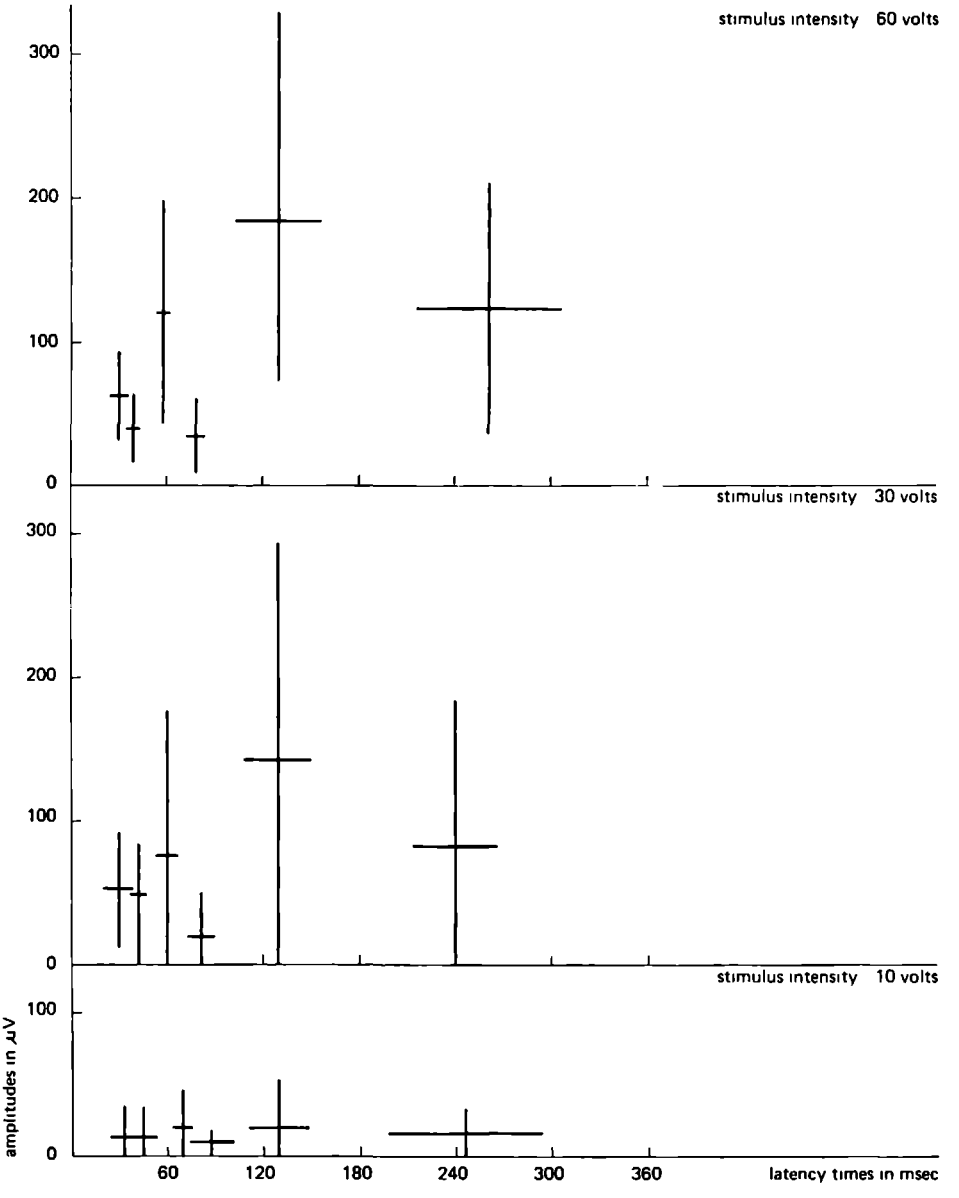

Fig. 3.28. Mean and standard deviations of amplitudes (vertical bars) and latency times (horizontal bars) of the peaks in *electrically* evoked potentials in the ipsilateral somatosensory cortex I and II at three different stimulus intensities.

The amplitudes in S I were very small, approximately 12 μV, while the potentials in S II had amplitudes of about 100 μV. The peaks with small latencies (< 50 msec) had small amplitudes and were not always present.

Mechanical stimulation

Mechanical noxious *stimulation* to the hind paw evoked in S I a potential with six peaks and with peak latencies of 29, 51, 100, 157, 250 msec (Fig. 3.24. above). The first one was not always present and was the smallest in amplitude.

The stimulation evoked in ipsilateral cortex II a potential with peak latencies of 18, 37, 55, 108, 182 and 325 msec (Fig.3.24 below). The amplitudes were between 40 and 125 μV. The largest ones were the last three waves. These last waves also increased the most in amplitude.

In the combined I/II lead peak latencies of 16, 35, 64, 141 and 267 msec were found (Fig. 3.25.). Here again the amplitudes of the later waves were the largest and the most influenced by stimulus intensity.

Electrical stimulation

Figures 3.26., 3.27. and 3.28. give the means and standard deviations of the peaks in the electrically evoked potentials in S I, S II and S I plus S II respectively.

The following peaks were found: an early small-amplitude peak at 19-29 msec in S I and S I/S II, another early small-amplitude peak at 27-38 in S I, S I/S II and S II, a peak which was small in S I but of large amplitude in S I/S II and S II, with rising latency of 43, 57 and 65 msec respectively; then a peak with latencies of 61-78 and 92 msec respectively and a large amplitude in S II; the next peak had large amplitudes in all leads and the shortest latency in S I, the longest in S II while the S I/S II lead was intermediate; the same applies to the next two peaks.

3.3.2.3.2. Discussion and conclusion

In the ipsilateral cortex I and II the potentials evoked by the three methods of stimulation are similar concerning their peak latencies, the latency times of the *tooth-pulp* evoked potentials being shortest and those of the *mechanically* evoked potentials longest. Here the distance of the stimulation site from the recording site and the time between stimulus onset and actual *skin stimulation* play a role. The amplitudes of the *electrically* evoked potentials are larger than those with the *tooth-pulp* and *mechanical*

stimulation methods. Comparison with contralateral cortex shows that the amplitudes of the *mechanically* evoked potentials in the contralateral cortex I are much larger, in the contralateral cortex II, however, they are almost the same. The amplitudes of the potentials of the S I/II combined recording are quite the same in both ipsilateral and contralateral cortex.

The latency times, on the other hand, are much larger on the ipsilateral than on the contralateral side.

In pigs the sensory evoked potential in the ipsilateral sensory cortex II has longer latencies than in the contralateral cortex (WOOLSEY and FAIRMAN 1946). In man the amplitude of the nociceptive thermally evoked potential is smaller in the ipsilateral S I than in the contralateral S I (WOOLSEY and FAIRMAN 1946).

Concerning the latency times: contralateral has earlier peaks than ipsilateral in S I (CHATRIAN et al. 1975) in general approximately 10 msec (CARMON et al. 1976).

The impulses have to be conducted over a longer time than on the contralateral side. This was found both in our study and by other investigators.

In the ipsilateral cortex I and II mainly the later waves are present. It also appears that the ipsilateral cortex is involved in nociception because large amplitudes evoked by Aδ and C fiber stimulation are present.

3.4. General discussion and conclusion

If the data on latency times of potentials recorded in the peripheral and central nervous systems are taken into account a succesive shift in latencies of the evoked peaks from the periphery to the brain emerges.

The latency times for the tooth-pulp evoked potentials in the different brain centers are compared in table 3.1. The first peak has a latency of 19-38 msec with a double peak in the contralateral sensory cortex II (SSCL II). The second peak with a latency of 42-59 msec is missing in the nucleus reticularis gigantocellularis. The third one, 66-79 msec is missing in the ipsilateral sensory cortex II. The next one, the fourth has a latency of 98-141 msec, the fifth a latency of 134-320 msec. In the subcortical areas and somatosensory cortex I on the opposite side a sixth

peak with a latency of 228-365 msec is seen and a very late component at 376 msec in amygdala and SSCL I.

No successive increase in peak latency is found from lower brain centers to higher brain centers. The peaks with latencies < 100 msec seem to appear first in the amygdala and hypothalamus and then in the nucleus reticularis gigantocellularis (NRGC), thalamus and contralateral cortex. For the later components the contralateral cortex seems to be the first place, then NRGC, then hypothalamus and amygdala, thereafter thalamus, and lastly the ipsilateral cortex.

Needle-prick stimulation to the right hind paw gives almost the same potential in the brain regions (Table 3.2.). There is a very early peak with a latency of 10 msec in the spinal cord and 21 msec in the contralateral cortex. The second peak is comparable with the first one of the tooth pulp evoked potential; 15 msec latency in the spinal cord, 37 msec in ipsilateral cortex II; the third: 27 msec in spinal cord, 64 msec in ipsilateral sensory cortex I/II; the fourth: 64 msec in spinal cord, 108 msec in ipsilateral cortex; the seventh: 140 msec in spinal cord, 325 msec in ipsilateral cortex. The peaks appear first in the contralateral somatosensory cortex I and sometimes also very early in the ipsilateral sensory cortex I; then in the subcortical areas and lastly in the sensory cortex II both left and right and in the amygdala.

These peaks are comparable with the later peaks in tooth-pulp evoked potentials.

Table 3.3. shows the mean peak latency potentials to electrical hind paw stimulation. The number of peaks is comparable with that produced by mechanical stimulation. The latencies, however, are a little shorter; seven peaks are present with successive latencies in the brain centers of 9-29, 18-38, 27-65, 43-92, 88-174, 140-319 and 255-382 msec.

Here also the potentials seem to occur first in the contralateral sensory cortex I, but sometimes also in the ipsilateral sensory cortex I, and then in the subcortical areas, the thalamus, the hypothalamus and amygdala being usually the first to show a response. The ipsilateral sensory cortex II is the last brain region where a response is seen. The wave form of the potentials evoked by the different stimuli, tooth-pulp, mechanical (needle) and electrical, are the same. The differences are seen in the latency times, shortest for tooth-pulp and longest for mechanical stimulation. This has also been found in man, where the mean latencies of some

earlier peaks of the somatosensory evoked potentials to mechanical stimulation were significantly longer than those of the corresponding peaks of the somatosensory evoked potentials (SEP) to electrical stimulation (NAN'NO et al. 1978).

As can be seen in tables 3.1., 3.2. and 3.3., the conclusion is that the peaks in the potential are most probably generated by afferents which differ in their conduction velocities. The very early peaks, 50 msec, seem to be evoked by Aβ and Aγ fibers, the next two peaks, with latencies between 50 and 182 msec, by Aδ fibers and the following peak by C fiber stimulation. The subsequent peaks are probably generated in the brain and may be a cerebral response to the noxious stimulation.

In man, different effects of peripheral ischemia on each somatosensory evoked potential peak suggest that individual SEP components may be selectively mediated through different primary afferent fibers (YAMADA et al. 1978). Many researchers have used the SEP of the cortex as a measure of pain perception in man (DAWSON 1947; JOHNSON et al. 1975). Painful thermal stimuli have been shown to evoke especially two late components, 130-190 msec and 230-300 msec, in man (CARMON et al. 1976).

With increasingly noxious laser stimulation in man, a linear relationship has been found between subjective verbal response and evoked potential amplitude (COGER et al. 1980). Percutaneous electrical noxious stimulation also evokes cortical potentials in man; the amplitudes of the late waves of these potentials are an objective correlate of the subjective verbal response (LAVINE 1976; STOWELL 1977; BUCHSBAUM et al. 1977; ARBUS et al. 1978). Tooth-pulp evoked potentials represented the first objective, measurable nonverbal signs of central events which are concommittant with acute experimental pain in man (CHATRIAN et al. 1975).

The late waves, 80-140 and 170-260 msec, (ROHDEWALD et al.1980), too are highly correlated with the verbal reports of pain in human subjects (CHATRIAN et al. 1975; FRANZEN and OFFENLOCH 1969; SPRENG and ICHIOKA 1964). In patients with congenital insensitivity to pain no tooth-pulp potentials could be evoked (CHATRIAN et al. 1975).

The amplitudes of the late waves even give an indication of susceptibility or nonsusceptibility to stress and of pain-sensitive and pain-insensitive interindividual variations (BUCHSBAUM et al. 1981). This is probably one of the causes of the great variability in our results.

It must be pointed out in this connection that besides an interindividual difference in pain sensitivity the differences in resistance of the brain electrodes may also be involved. In human subjects an increase in stimulus frequency does increase the evoked amplitude without an increase in pain as reported verbally (CHAPMAN et al. 1981). In our experiment we used only one stimulus frequency.

It can be generally concluded that the late waves in the evoked potentials are the representation of noxious messages in the brain. Reduction of the amplitude of these late waves is indicative of decreased pain perception in both man and animals.

Since no particular brain region can be pointed out as 'pain center', because many centers of the central nervous system are involved in pain perception (BIEDENBACH et al. 1979), all the above mentioned regions are important in this study.

The stimuli with high intensities (> 40 volt and > 150 gram force in mechanical stimulation) activate nociceptive Aδ and C fibers and evoke large potentials in all these brain structures. These stimuli are noxious in character. This appears the more likely since immediately after starting the stimulation a heart rate increase and peripheral circulatory collapse, as demonstrated by light pletysmography, are observed. This is probably a consequence of epinephrine release.

These high-intensity stimuli were therefore used in the experiments with anesthetics, as presented in the next chapter.

Table 3.1. TOOTH-PULP STIMULATION

NCG		27		70	108	134	308	
THALAMUS		30	46	79	130	211	365	
HYPOTHALAMUS		24	42	66	106	178	291	
AMYGDALA		19	46	77	117	183	274	376
SSCL I		30	52	75	98	145	228	376
SSCL II	27	38	56	72	109	199		
SSCR I		30	59	79	116	247		
SSCR II		34	58		141	320		

Latency times of tooth-pulp evoked potentials in different brain centers.

Table 3.2. MECHANICAL STIMULATION

SPINAL CORD	10	15	27	64	98	140	
NRGC	15		42	91		222	
THALAMUS		30	46	77	137	210	300
HYPOTHALAMUS		35	57	90	150	245	384
AMYGDALA		35	79	139	169	278	400
SSCL I	21	29	38	52	121	210	
SSCL I/II	16	25	38	62	132	234	
SSCL II	21	37	60	111	163	250	
SSCR I		29	51	100	157	250	
SSCR I/II	16	35	64		141	267	
SSCR II	18	37		108	182	325	

Latency times of mechanically evoked potentials in different brain centers.

Table 3.3. ELECTRICAL STIMULATION

SPINAL CORD	9	18	27	43	88	140		
NRGC	20	28	35	72	144	220	382	
THALAMUS	20	33	48	76	119	165	300	
HYPOTHALAMUS	20	33	46	67	93	125	203	354
AMYGDALA		33		74	120	181	324	
SSCL I	24	30	140	55	101	160	283	
SSCL I/II	24	35	55	76	124	156	260	
SSCL II	23	31	39	56	122	177	255	
SSCR I	19	27	43	61	108	230		
SSCR I/II	29	38	57	78	128	262		
SSCR II		38	65	92	174	319		

Latency times of electrically evoked potentials in different brain centers.

CHAPTER 4

EFFECTS OF ANESTHETICS ON SOMATOSENSORY EVOKED POTENTIALS

4.1.1. General Introduction

Anesthetics can block impulse propagation in nerve fibers but, despite this, the available evidence points to the synapse as the primary site of attack (PATON and SPEDEN 1965). It thus seems probable that, in general, anesthetics exert a double action at synapses, reducing both the amount of transmitter release and the sensitivity of the postsynaptic membrane to the transmitter in the case of acetylcholine (JENKINS 1969). There are indications however, that anesthetics may vary as to the proportions in which these two actions are manifested (PATON and SPEDEN 1965).

Neurophysiological alterations involving depression of synaptic transmission in specific central nervous system sites during anesthesia have received attention (KING 1956); it is suggested that the reticular activating system is easily depressed by anesthetics (MAGOUN 1963).

Anesthetics and analgesics inhibit the conduction of impulses along the nociceptive pathway merely by blocking synaptic transmission. If these synapses are blocked, peripheral and nociceptive stimulation does not reach the central brain and no potentials in the higher brain centers, e.g. the cortex, are found.

The effects of lidocaine (a local anesthetic), nitrous oxide and halothane, two barbiturates (pentobarbital and thiopental), ketamine, fentanyl and two sedatives (droperidol and xylazine[11]) on the somatosensory evoked potential are presented in this chapter.

4.1.2. Materials and methods

The dogs were used for these experiments as described in Chapter 2.

Both before and after the drug administration we used 60 volt and 1 msec for the *electrical stimulation* and 400 gram for the *mechanical stimulation*. Since the amplitudes differed among the dogs the 'blank'

[11]) Rompun®, Bayer A.G.

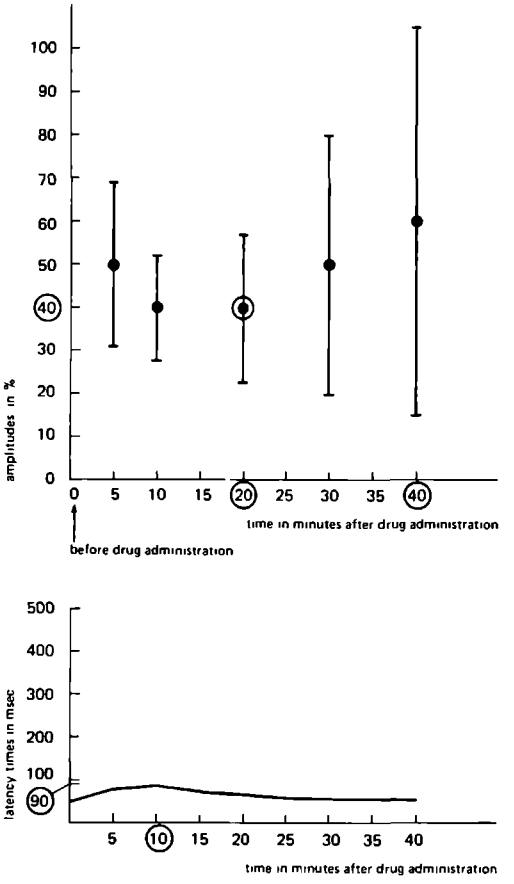

Fig. 4.1. Example of calculation of some characteristic figures showing the effect of an anesthetic on the evoked potential.
The encircled figures are given in the table in this chapter, viz.: the latency time before the anesthetic was administered, the maximum reduction found (40), the longest time for which this reduction was maintained (20), the time at which the reduction was no longer significant (40), the maximum change in latency (90) and the time at which this change was present (10).

amplitude was set to 100 and the percentage changes calculated. At successive times over a period of not more than 180 minutes after drug administration the evoked potentials were recorded. Only the maximum change in amplitude is reported. If for example, at 5 and 10 minutes the same maximum reduction was found, then only the longer time is given.

Fig. 4.1. shows the way in which the tables in this chapter are composed. This applies to all the tables excepting those for the experiments in which N_2O and halothane were used.

4.2. Effects of local anesthetics on the SEP

4.2.1. Introduction

Local anesthetics act on the nerve cell membrane in such a way that transport of sodium ions through this membrane is inhibited, with the result that no stimulus can be transmitted along the nerve fiber. Local anesthetics, thus, block the conduction of impulses via the peripheral nerves. The small, thin nerve fibers with no myelin sheath are affected earlier by local anesthetics than the thick, heavily myelinated fibers (HALL 1967). After injection of a local anesthetic the pain fibers are the first to be blocked, followed in succession by the temperature, tactile and motor fibers. Sometimes substances are added to the injection solution which cause the neighbouring blood vessels to contract, so that the local anesthetic is less rapidly carried away and its effect lasts longer. As a rule epinephrine is used for this purpose.

In our experiments we used 2% lidocaine with 0.002% epinephrine. We injected 2 ml of this solution subcutaneously at the places where electrical or mechanical stimulation was to be applied. Before each injection and twice after it the SEP were measured after an identical painful stimulus. In this paragraph the amplitudes after local anesthesia are reported as percentage of the 'blank' value, and also the changes in latency time.

4.2.2. Results

As described in Chapter 3, the potentials with different latency times are correlated with the differences in conduction velocity of the peripheral fibers, and hence with the thickness and modality of these fibers.

This is the reason why potentials with the same latencies from various brain regions are grouped together.

In table 4.1., reading from left to right, we note the brain region, the mean latency time, the maximum percentage reduction attained and the maximum change in peak latency following electrical stimulation of the hind paw.

Potentials with a latency time of less than 45 msec showed no significant reduction of amplitude, but they did show an appreciable increase in latency time.

Potentials with a latency longer than 45 msec were reduced to $^1/_3$rd or less of their initial amplitude in all brain regions. It is worthy of note that the potentials with latencies longer than 80 msec were reduced to a greater degree than those with latencies between 45 and 80 msec. With the exception of the very late potentials with latencies longer than 280 msec, the latencies were greatly increased and sometimes almost doubled.

Table 4.2. shows the corresponding results with mechanical stimulation. Looking first at the potentials with latency times shorter than 50 msec, we see that not only were most of the amplitudes not significantly reduced but also the latencies were unchanged.

The potentials with latencies between 50 and 150 msec were significantly reduced in amplitude, in general halved. The latency times of these potentials increased in the subcortical but not in the cortical structures.

The potentials with latencies longer than 150 msec were greatly reduced in amplitude, to $^1/_5$th or less, while the latency times were lengthened in the subcortical structures and shortened in the amygdala and cortex.

4.2.3. Discussion and conclusion

As pointed out in Chapter 3, the potentials with latency times shorter than 50 msec have their origin in stimulation of the fast-conducting heavily myelinated nerve fibers, which are not involved in pain perception. Lidocaine influences the conduction of impulses in these fibers only to a minor degree, as shown by the fact that there is practically no significant effect on amplitude and latency of these potentials to be seen, either with mechanical or with electrical stimulation.

The potentials with latency times between 50 and 140 msec, originating

Table 4.1. EFFECTS OF SUBCUTANEOUS INJECTION OF LIDOCAINE AT THE SITE OF *ELECTRICAL* STIMULATION ON THE SEP

BRAIN REGION	PEAK LATENCY BEFORE INJECTION IN MSEC	MAXIMAL REDUCTIONS IN PERCENTS	SIGNIFICANCE	MAXIMAL PEAK LATENCY CHANGE IN MSEC
somatosensory I/II contralateral	21	55	N.S.	25
N R G C	34	42	N.S.	44
somatosensory I/II ipsilateral	33	65	N.S.	39
N R G C	69	24		84
Thalamus	58	26		104
Hypothalamus	47	10		76
Amygdala	65	19		93
SSC I/II contral.	53	20		60
SSC I/II ipsil.	56	32		56
N R G C	133	34		189
Thalamus	117	11		152
Hypothalamus	110	14		226
Amygdala	96	5		171
SSC I/II contral.	110	32		134
SSC I/II ipsil.	135	18		112
Thalamus	270	21		309
Hypothalamus	204	5		298
SSC I/II contral.	301	7		242
SSC I/II ipsil.	271	5		263
Hypothalamus	336	10		372
Amygdala	400	5		384

N.S. = Not Significant

Vertically the potentials with the same latency times (mean of five dogs) in the different brain regions are grouped together.
Horizontally the maximum reduction in amplitude (mean of five dogs) and the maximal change in latency times (mean of five dogs), are shown.

Table 4.2.EFFECTS OF SUBCUTANEOUS INJECTION OF LIDOCAINE AT THE SITE OF *MECHANICAL* STIMULATION ON THE SEP

BRAIN REGION	PEAK LATENCY BEFORE INJECTION IN MSEC	MAXIMAL REDUCTIONS IN PERCENTS	SIGNIFICANCE	MAXIMAL PEAK LATENCY CHANGE IN MSEC
Thalamus	17	50	N.S.	28
SSC I/II contral.	25	84	N.S.	28
N R G C	36	34		54
Thalamus	34	37		37
Hypothalamus	48	53	N.S.	46
SSC I/II contral.	42	103	N.S.	43
SSC I/II ipsil.	33	54	N.S.	38
N R G C	94	17		141
Thalamus	68	57		176
Hypothalamus	81	50		85
Amygdala	89	45		112
SSC I/II contral.	65	42		56
SSC I/II ipsil.	68	41		63
Thalamus	125	57		176
Hypothalamus	133	45		141
Amygdala	135	23		179
SSC I/II contral.	131	55		142
SSC I/II ipsil.	127	28		136
N R G C	212	8		259
Thalamus	154	18		173
Hypothalamus	241	14		293
Amygdala	213	21		160
SSC I/II contral.	269	2		252
SSC I/II ipsil.	252	6		230

N.S. = Not Significant. For explanation: see Table 4.1.

from Aδ fibers, as stated in Chapter 3, are greatly reduced in amplitude and their latencies also increase somewhat. This is in agreement with the findings of GEHRIG et al. (1981). In human subjects,too,it has been found that the 100-150 msec component following painful stimulation of the tooth pulp under local anesthesia is reduced to 25% of its initial value.

In our study the component with latency time between 150 and 275 msec was very greatly reduced in amplitude, to 10% of its initial value (C fiber stimulation). This is also in agreement with the results of GEHRIG et al. (1981).

The very late component, which is only present in the amygdala and hypothalamus, was also reduced, to 10%, in our investigation. In human subjects this component is less strongly reduced, to 35%.

Local anesthesia produces a large reduction in the amplitudes of those components of the evoked potential which originate from stimulation of Aδ and C fibers. Since these fibers play an important part in pain conduction it may be concluded that local anesthesia is highly effective for elimination of pain in animals.

4.3. Effects of nitrous oxide and halothane on the SEP

4.3.1. Introduction

Nitrous oxide was the first inhalation anesthetic used in dentistry. For a sufficiently deep general anesthesia the inhaled mixture must contain at least 95% of nitrous oxide, and this allows only 5% for oxygen. For this reason nitrous oxide is used together with oxygen as carrier-gas for other anesthetics. Even at the low concentrations used in this way it is a good analgesic (CHAPMAN et al. 1943). As anesthesia with nitrous oxide becomes deeper the amplitudes of the SEP in the central brainstem decrease, while the latency times remain unchanged(DAVIS et al. 1957 and 1958).

Halothane, an inhalation anesthetic of more recent introduction, is not a powerful analgesic (JENKINS 1969) and it does not influence the nerve-muscle junctions (SABAWALE and DILLON 1958).

4.3.2. Materials and methods

The dogs were used as described in Chapter 2. To begin with a 'blank' SEP, i.e. without use of anesthetics, was recorded. Then a gas mixture with approximately 33% oxygen and 67% nitrous oxide was administered, and after the animal had been ventilated for 15 minutes with this mixture a second SEP was recorded, the stimulus having, of course, the same intensity as the first one. After this, in the same session 1.5% halothane was added to the gas mixture and again a SEP was recorded. The same thing was done 10 minutes after 3% halothane, 5 minutes after 5% halothane and 15 minutes after 2% halothane. The last SEP was recorded after the dog had been ventilated for 30 minutes with 100% oxygen.

4.3.3. Results

The potentials with the same latency times in the various brain regions are placed together in tables 4.3. and 4.4. These tables show, from left to right, the brain region, the latency time of the potential before anesthetic administration and further the amplitude (as percentage of the blank value) for each of the SEP recorded after the different anesthetic mixtures and intervals, as detailed above.

Table 4.3. shows the corresponding values for the electrically evoked potentials (EEP). The potentials with the shortest latency times did not decrease significantly in amplitude when nitrous oxide was administered.

The following potentials, with latencies of 28-52 msec, did not decrease significantly in amplitude after nitrous oxide administration whereas an increasing number of brain regions showed a significant influence on the recorded potentials as the concentration of halothane in the gas mixture was increased. This does not apply to the ipsilateral somatosensory cortex I. The potentials with latencies between 36 and 91 msec were significantly reduced by nitrous oxide in the N R G C and thalamus, and by 1.5% halothane also in the hypothalamus. Halothane at 3% caused a significant reduction of these potentials in all subcortical regions; with 5% and 2% halothane there was a significant reduction in all brain regions. The latency times remained the same or increased somewhat after nitrous oxide and halothane, the greatest increase being noted in the contralateral cortex.

The potentials with latency times between 92 and 125 msec had their

Table 4.3. EFFECTS OF N_2O, HALOTHANE AND O_2 ON THE *ELECTRICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	15 MIN N_2O 67%		10 MIN 1½% HALOTHANE		10 MIN 3% HALOTHANE		5 MIN 5% HALOTHANE		15 MIN 2% HALOTHANE		30 MIN 100% O_2	
		amp.**	lat.***	amp.	lat.	amp.	lat.	amp.	lat.	amp.	lat.	amp.	lat.
SSC II contral.	18	84*	17	48*	19	55*	21	85*	21	86*	29	69*	24
N R G C	18	57*	19	48	20	44	21	14	15	42	26	84*	22
SSC I contral.	21	71*	20	59*	22	74*	23	82*	24	57*	25	92*	23
SSC II contral.	27	81*	23	55*	26	58*	30	79*	36	47*	37	80*	31
SSC I ipsil.	36	43	40	56*	35	75*	31	52*	50	101*	41	76*	35
SSC II ipsil.	32	111*	33	76*	28	74*	35	64	51	111*	52	94*	33
N R G C	36	57*	39	60*	36	58*	35	63*	36	57	42	109*	35
Thalamus	38	50*	38	41	43	28	44	31	59	47	78	61*	33
Hypothalamus	43	41	45	51	49	52	50	15	52	42	84	66*	51
Amygdala	47	77*	67	85*	71	53	52	46	88	61*	96	88*	65
SSC I contral.	28	50*	27	57*	27	74*	30	66*	36	83*	35	88*	30
SSC II contral.	36	70*	29	81*	34	87*	45	100	51	98	69	100*	38
SSC I ipsil.	52	77*	66	101*	60	100*	87	60	111	71	85	120*	59
N R G C	74	35	93	69*	105	42	70	20	78	40	104	90*	95
Thalamus	63	42	61	39	67	37	74	32	105	32	109	60*	52
Hypothalamus	74	71*	82	24	86	47	89	36	83	37	106	63*	78
Amygdala	91	100*	89	104*	39	63*	114	45	100	45	127	122*	118
SSC I contral.	49	94*	58	82*	56	90*	58	38	65	50	63	104*	50
SSC II contral.	56	76*	54	80*	60	73*	77	42	77	72	136	93*	59
SSC I ipsil.	86	101*	114	71*	125	63*	131	14	161	43	134	77*	77
SSC II ipsil.	70	101*	113	93	64	73*	123	51	144	29	119	105*	73
N R G C	118	21	166	35	179	41	138	31	129	35	164	82*	161
Thalamus	107	30	104	27	102	23	121	16	143	33	142	89*	95
Hypothalamus	105	78*	121	51	124	43	130	37	123	56	224	96*	138
Amygdala	108	43	132	64	124	39	143	19	137	38	190	49*	119
SSC I contral.	92	67*	87	65	96	58	96	10	110	21	96	98*	103
SSC II contral.	103	35	95	41	98	53	134	29	135	29	186	80*	103
SSC I ipsil	121	64*	150	59	169	47	183	25	239	69	214	79*	121
SSC II ipsil.	122	79*	210	75	129	73	219	13	234	5	163	63*	153

Table 4.3. EFFECTS OF N_2O and O_2 ON THE *ELECTRICALLY* EVOKED POTENTIALS *(continued)*

BRAIN REGION	PEAK LAT T BEFORE	15 MIN N_2O 67%		10 MIN 1½% HALOTHANE		10 MIN 3% HALOTHANE		5 MIN 5% HALOTHANE		15 MIN 2% HALOTHANE		30 MIN 100% O_2	
		amp.**	lat.***	amp.	lat.	amp.	lat.	amp.	lat.	amp.	lat.	amp.	lat.
N R G C	174	12	173	68*	293	18	188	12	163	25	165	56*	212
Hypothalamus	167	78*	189	29	157	13	187	15	189	30	276	76*	171
Amygdala	170	33	207	24	202	9	236	30	205	8	279	63*	171
SSC I contral.	138	20	125	60*	135	47	143	24	140	69	140	55*	140
SSC II contral.	170	57*	142	61*	147	89*	190	30	210	62	248	115*	160
SSC I ipsil.	197	40	239	16	232	27	272	33	264	78	291	69*	115
N R G C	225	10	302	7	325	37	209	17	170	20	209	60*	282
Thalamus	271	33	249	18	204	24	256	30	248	54	270	71*	220
Amygdala	268	8	306	36	306	16	317	30	271	20	245	72*	261
SSC I contral.	252	49	246	51	263	32	239	13	255	24	258	74*	247
SSC II contral.	294	32	240	44	247	48	286	35	253	51	349	75*	238
SSC I ipsil.	292	75*	280	48	314	54	286	13	335	75	310	71*	253
SSC II ipsil.	295	51*	334	39	302	33	344	13	344	24	368	54*	337
N R G C	345	25	343	33	338	37	336	37	310	42	310	71*	362
Thalamus	445	70*	386	25	365	20	390	30	384	72	243	74*	337
Hypothalamus	348	61*	334	7	312	15	319	6	385	42	344	45	335
Amygdala	382	20	418	23	389	14	344	30	392	17	430	59*	395
SSC I ipsil.	406	17	323	32	404	32	379	25	398	18	415	79*	370

* = not significant

** = amplitude in %

*** = latency time in msec

Vertically the potentials with the same latency times (mean of six dogs) from different brain centers are grouped together.
Horizontally the maximum reduction in amplitudes (mean of six dogs) and maximal change in latency times (mean of six dogs) after the N_2O and different concentrations of halothane are shown.

Table 4.4. EFFECTS OF N_2O, HALOTHANE AND O_2 ON THE *MECHANICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	20 MIN N_2O 67%		10 MIN 1½% HALOTHANE		10 MIN 3% HALOTHANE		5 MIN 5% HALOTHANE		15 MIN 2% HALOTHANE		30 MIN 100% O_2	
		amp.**	lat.***	amp.	lat.	amp.	lat.	amp.	lat.	amp.	lat.	amp.	lat.
Amygdala	25	52*	49	26	35	50*	57	13	29	39	68	30	25
SSC I contral.	24	49	26	31	22	51*	25	33	25	59*	26	93*	25
SSC II contral.	22	19	19	57*	28	71*	32	46	22	54*	22	114*	18
N R G C	37	41	40	19	48	53*	42	50*	44	14	49	45	40
Thalamus	38	64*	50	27	54	22	62	42	54	27	41	60*	42
Hypothalamus	46	30	58	21	76	16	94	29	110	27	103	73*	55
SSC I contral.	33	62*	36	53*	34	41	35	36	39	45	37	86*	33
SSC II contral.	32	58*	25	51	32	77*	47	56*	40	67*	30	87*	31
SSC II ipsil.	38	44	41	65*	44	48	43	53*	50	83*	55	80*	37
N R G C	76	32	73	9	95	15	65	13	98	7	90	85*	75
Thalamus	69	77*	84	32	94	23	121	36	96	45	81	70*	84
Hypothalamus	74	51*	98	40	110	10	123	15	124	46	119	83*	90
Amygdala	60	28	104	18	79	25	104	9	136	31	82	82*	70
SSC I contral.	54	63*	58	30	61	20	67	26	63	56*	61	104*	62
SSC II contral.	47	84*	52	62*	72	33	85	35	67	39	54	83*	60
SSC II ipsil.	77	55*	88	35	98	26	119	23	102	61*	100	105*	92
N R G C	107	23	123	11	150	9	123	3	153	36	188	98*	107
Thalamus	95	59*	109	19	136	39	132	30	142	60*	157	80*	87
Hypothalamus	119	28	159	22	169	20	185	20	178	23	159	65*	130
Amygdala	105	27	196	25	161	22	153	1	180	13	130	64*	118
SSC I contral.	106	66*	102	23	104	25	108	11	101	44	108	64*	105
SSC II contral.	81	60*	93	58*	128	38	147	30	128	58*	98	65*	93
SSC I ipsil.	91	44	136	26	138	39	135	30	138	71*	113	77*	100

Table 4.4. EFFECTS OF N_2O, HALOTHANE AND O_2 ON THE *MECHANICALLY* EVOKED POTENTIALS *(continued)*

BRAIN REGION	PEAK LAT T BEFORE	20 MIN N_2O 67%		10 MIN 1½% HALOTHANE		10 MIN 3% HALOTHANE		5 MIN 5% HALOTHANE		15 MIN 2% HALOTHANE		30 MIN 100% O_2	
		amp.**	lat.***	amp.	lat.	amp.	lat.	amp.	lat.	amp.	lat.	amp.	lat.
N R G C	168	18	178	16	217	12	174	0	181	66*	177	103*	142
Thalamus	134	49	156	13	188	29	155	0	154	46	155	80*	182
Hypothalamus	143	15	275	15	302	20	320	21	291	36	265	65*	281
Amygdala	163	24	242	18	222	22	206	23	222	34	297	72*	177
SSC I contral.	155	34	150	34	151	25	153	22	141	70*	139	80*	162
SSC II contral.	175	52	187	28	213	17	232	25	225	30	199	57*	167
SSC I ipsil.	195	35	187	22	250	23	230	20	270	41	228	50*	205
SSC II ipsil.	150	69	145	41	147	29	172	22	188	34	145	97*	164
N R G C	302	9	291	12	378	1	313	0	383	33	387	91*	314
Thalamus	277	24	284	34	283	38	269	34	312	47	282	60*	270
Amygdala	270	13	333	12	322	11	311	9	333	37	300	65*	282
SSC I contral.	258	10	183	7	253	20	253	13	241	60*	350	55*	255
SSC II contral.	368	32	293	43	307	26	316	17	323	43	269	47	276
SSC I ipsil.	335	24	278	17	332	25	289	0	317	33	304	66*	330
SSC II ipsil.	350	49	277	43	299	18	351	14	354	34	343	67*	388
Thalamus	437	8	384	0	387	11	382	10	384	33	376	45	390
Hypothalamus	442	14	413	2	388	4	398	10	388	15	383	32	399
Amygdala	381	30	402	25	380	14	368	23	385	32	368	49*	372

* = not significant

** = amplitude in %

** = latency time in msec

For explanation: see Table 4.3.

amplitudes significantly reduced by nitrous oxide in the N R G C, thalamus, amygdala and contralateral sensory cortex II; with 1.5% halothane the reduction of the potential in the amygdala was no longer significant; with 3% halothane there was a significant reduction in all brain regions tested, except in the contralateral sensory cortex I and the ipsilateral cortex II; with 5% halothane there was a significant reduction in all brain regions; this was also the case with 2% halothane, although the reduction was then less marked. With 100% oxygen a significant reduction, to 50%, remained only in the amygdala. The latency time of all these potentials increased as the concentration of halothane in the gas mixture increased.

The potential with a latency time of 138 to 197 msec, which was not present in all brain regions, was not significantly reduced by nitrous oxide in the hypothalamus and contralateral sensory cortex II. In this case too the amplitude increased again in the N R G C and contralateral cortex I when the halothane concentration was 1.5%; with 3% halothane only the amplitude in the contralateral cortex II was not significantly reduced; with 5% and then 2% halothane the amplitudes in all brain regions were significantly reduced; while with 100% oxygen there was no longer a significant reduction.

The next series of potentials, with latencies of 225 to 295 msec, showed a reduction in amplitude by nitrous oxide in subcortical and contralateral cortical regions; these potentials were significantly reduced by halothane but returned to practically normal amplitudes after 100% oxygen. The latencies of these potentials showed variable changes, but with a tendency towards prolongation.

The last series of potentials showed, except in the thalamus and hypothalamus, a significant reduction in amplitude by nitrous oxide, and in all regions a significant reduction by halothane. Here again the changes in latency time were variable.

Mechanical stimulation with a needle produced, under the influence of nitrous oxide with or without halothane, changes of amplitude and latency as shown in table 4.4. The potentials with latencies shorter than 50 msec did not have their amplitudes greatly reduced by nitrous oxide or halothane, while their latency times also showed little change.

The potentials with latencies between 50 and 80 msec were still not much reduced in amplitude by nitrous oxide; with 3% and 5% halothane, how-

ever, there was a very marked reduction, and with the lower concentrations a nonsignificant reduction was discernible here and there in the cortical regions. The latencies of these potentials also became longer under the influence of nitrous oxide and halothane.

The next series of potentials, from 80 to 120 msec underwent marked reduction by nitrous oxide, except in the thalamus and contralateral cortex. Halothane produced a still greater reduction in amplitude, although in the contralateral cortex II high concentrations were required for this effect.

The 130-200 msec potentials were significantly reduced both by nitrous oxide and by halothane, although with 2% halothane the effect in the contralateral sensory cortex I was no longer significant. Here again the latency times tended to increase. All the later potentials were significantly reduced by nitrous oxide and halothane, while the changes in latency time were variable.

4.3.4. Discussion and conclusion

Both nitrous oxide and halothane had a marked effect on both mechanically and electrically evoked potentials in all brain regions. The mechanically evoked potentials seemed to be more reduced than the electrically evoked ones; this may be possibly be related to the intensity of stimulation, which was greater with the electrical stimulus. As the latency times of the potentials increased the reduction of their amplitudes increased also. The subcortical regions seemed to be more strongly affected by these anesthetics than the cortical regions.

SPENCER et al. (1976) found in the N R G C of cats a reduction of 70% in amplitude after nitrous oxide anesthesia this is in good agreement with our observations; the N R G C is sensitive to both nitrous oxide and halothane. DAVIS et al. (1957) found, in the same species, a reduction after nitrous oxide of 50% in the reticular formation and 25% in the thalamus, this last, however, being less than what we observed in our dogs. The hypothalamus and the amygdala seem to be less affected by nitrous oxide and halothane than the N R G C and the thalamus. The cortex is the least affected, although a considerable reduction in amplitude is seen with high concentrations of halothane; this has also been observed in man (TACHIBANA 1975; CLARK et al. 1970).

In general it can be said that nitrous oxide has a strong effect on the

reticular formation and the thalamocortical connections, and a weaker effect on the hypothalamus, amygdala and neocortex.

Whereas we were unable to find in other studies any mention of the effect of halothane on evoked potentials, our study has shown that halothane in higher concentrations produces a very considerable reduction in amplitude of the potentials in all brain regions. Nitrous oxide and higher concentrations of halothane are thus good agents for ensuring satisfactory elimination of pain in dogs.

The reduction in amplitude of evoked potentials is practically abolished by administration of 100% oxygen for 30 minutes.

4.4. Effects of barbiturates on the SEP

4.4.1. Introduction

Barbituric acid derivatives have been known since the beginning of this century. The various barbiturates differ among themselves in their duration of action.

Barbiturates act on the synapses in the CNS but some effects on the peripheral nerves and on the neuromuscular system have also been demonstrated (PRICE and DRIPPS 1970; NGAI 1963; FELDBERG and FLEISCHHAUER 1965; THESLEFF 1956).

The unconsciousness caused by barbiturates is due primarily to blockade of the reticular activating system (MORUZZI and MAGOUN 1949). When true unconsciousness is produced the pain sensation is also eliminated (CLUTTON-BROCK 1960). Barbiturates block chiefly the motor areas in the cortex, and for this reason are frequently used as antiepileptic agents. Suppression of the sensory areas in the cortex requires an increase of dosage until unconsciousness is produced (ALEXANDER 1969).

The following paragraph describes the effects of two doses of thiopental and pentobarbital (both in the form of their sodium derivatives) on the electrically and mechanically evoked potentials.

4.4.2. Results

The electrical and mechanical SEP were registered before and after i.v. administration of 30 mg/kg of pentobarbital. The amplitudes of the potentials before the injection were taken as 100 and the amplitudes subsequently found were reported as percentages of this 'blank' value. The

latency times were reported in msec.

In the tables (4.5. up to 4.12. inclusive) the potentials with more or less the same latency times in various brain regions are grouped together as before. Reading from left to right the successive columns indicate the brain region, latency time of the 'blank' SEP, smallest amplitude found after the barbiturate injection, significance of the decrease in amplitude, time after injection at which this smallest amplitude was found, time after injection at which the amplitude decrease was no longer significant, maximal peak latency change and time at which this was reached. Table 4.5. shows these values for *electrical* stimulation and 30 mg/kg pentobarbital i.v.

All the peaks with latencies < 40 msec in all brain regions and the 51 msec in thalamus were only nonsignificantly altered by pentobarbital. The latency times of these peaks became longer 20-30 msec after i.v. administration of pentobarbital.

The later waves gave the following results: in N R G C a reduction to 48% was seen in the 61 msec peak, progressing to 17% in the 202 msec peak. The amplitudes returned to their original values after 150 minutes. The latency times became longer after 45-80 minutes. In the thalamus similar effects were seen, although the reduction lasted only for 30-80 minutes.

In the hypothalamus no significant reduction was found, except for the very late component (417 msec). A prolongation of the latency was however, seen. The components of the SEP of the amygdala first decreased in amplitude and then increased slightly, but still remained below 39%. There was also a prolongation of latency times with its maximum between 80 and 180 minutes.

The potentials in the SSC I contralateral with latency times shorter than 45 msec w e r e not significantly changed. The later components in this brain region were strongly reduced to 9-15%. These maximum reductions were reached within 20 to 30 minutes after barbiturate injection, and after 100-180 minutes there was no longer any reduction. In the contralateral SSC I an increase in latency times was noted, also reached within 20-30 minutes.

The SEP of the contralateral cortex II, however, was decreased in amplitude to only 30-50% and regained its amplitudes after 80-100 minutes. In the ipsilateral cortex I there was first a reduction to 14% of the original amplitude; in the later components a 85% reduction was again present.

Table 4.5. EFFECTS OF PENTOBARBITAL (30 mg/kg i.v.) ON THE *ELECTRICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE		TIME AT WHICH THIS IS REACHED IN MINUTES	TIME AT WHICH A SIGNIFICANT CHANGE IS NOT PRESENT ANYMORE (MIN)	MAXIMUM PEAK LATENCY CHANGE IN MSEC	TIME AT WHICH THIS IS REACHED
SSC I contral.	19	80	N.S.	20		24	30
SSC II contral.	21	76	N.S.	20		29	30
SSC I ipsil.	23	64	N.S.	20		45	30
SSC I contral.	26	76	N.S.	20		36	30
N R G C	31	94	N.S.	20		36	20
Thalamus	39	29	N.S.	5		78	45
SSC I contral.	34	50	N.S.	30		49	20
SSC II contral.	33	63	N.S.	20		63	80
SSC I ipsil.	33	34	N.S.	20		51	20
SSC II ipsil	35	71	N.S.	20		61	30
Thalamus	51	93	N.S.	20		100	30
Hypothalamus	59	60		60	100	89	30
SSC I contral.	48	14		20	> 180	63	20
SSC II contral.	48	32		20	80	138	30
SSC I ipsil.	54	14		30	150	81	45
N R G C	61	48		60	> 180	80	80
Thalamus	72	36		20	30	136	45
Hypothalamus	87	62	N.S.	5		118	20
Amygdala	65	25		20	150	122	5
SSC II contral.	63	31		30	> 180	152	45
SSC I ipsil.	65	23		10	80	110	30
SSC II ipsil.	65	43		20	60	155	30
N R G C	129	23		20	180	162	80
Thalamus	106	28		30	45	224	30
Hypothalamus	122	82	N.S.	30	180	175	20
Amygdala	128	12		30	120	182	60
SSC I contral.	95	15		30	80	108	30
SSC II contral.	109	30		20	60	211	45
SSC I ipsil.	97	48		20	60	154	89
SSC II ipsil.	130	29		20	180	221	30

Table 4.5. EFFECTS OF PENTOBARBITAL (30 mg/kg i.v.) ON THE *ELECTRICALLY* EVOKED POTENTIALS *(continued)*

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME AT WHICH THIS IS REACHED IN MINUTES	TIME AT WHICH A SIGNIFICANT CHANGE IS NOT PRESENT ANY-MORE (MIN)	MAXIMUM PEAK LATENCY CHANGE IN MSEC	TIME AT WHICH THIS IS REACHED
N R G C	202	17	60	80	285	5
Thalamus	171	14	20	80	259	45
Hypothalamus	177	51 N.S.	30	80	290	30
Amygdala	173	39	30	80	231	45
SSC II contral.	179	55	20	100	305	80
SSC I ipsil.	167	43	20	80	205	80
Thalamus	284	20	20	80	373	30
Amygdala	248	34	30	100	322	30
SSC I contral.	203	10	30	100	221	45
SSC I ipsil.	228	33	5	180	252	80
SSC II ipsil	292	49	30	80	301	60
Thalamus	433	15	20	180	374	60
Hypothalamus	417	21	80	80	351	60
Amygdala	380	29	45	180	418	30
SSC I contral.	278	9	30	100	293	45
SSC II contral.	318	50	20	100	410	100
SSC I ipsil.	372	15	30		305	45

N.S. = Not Significant

Vertically the potentials with the same latency times (mean of six dogs) observed in different brain centers are grouped together.
Horizontally the maximum reduction (mean of six dogs) in amplitude, the time at which this reduction is reached (mean of six dogs), the time at which a significant reduction is no longer present, the maximum peak latency change (mean of six dogs) and the time at which this is reached (mean of six dogs), are shown.

Table 4.6. EFFECTS OF 30 mg/kg PENTOBARBITAL ON THE *MECHANICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME AT WHICH THIS IS REACHED IN MINUTES	TIME AT WHICH A NON-SIGNIFICANT CHANGE IS NOT PRESENT ANYMORE	MAXIMUM PEAK LATENCY CHANGE IN MSEC	TIME AT WHICH THIS IS REACHED
SSC I contral.	23	73 N.S.	10		27	20
SSC I contral.	28	56 N.S.	20		33	80
SSC II contral.	29	88 N.S.	10		34	20
SSC I ipsil.	31	57 N.S.	20		60	45
N R G C	36	22	10	30	41	45
Amygdala	39	27 N.S.	30		139	60
SSC I contral.	36	45 N.S.	20		46	80
SSC I ipsil.	45	8	30	120	165	45
SSC II ipsil.	38	57 N.S.	45		69	20
Thalamus	67	60 N.S.	20		139	30
Hypothalamus	67	32 N.S.	45		136	30
SSC I contral.	59	28 N.S.	30		68	80
SSC II contral.	52	51 N.S.	30		83	80
SSC I ipsil.	63	23	20	30	114	80
N R G C	92	20	45	180	126	100
Amygdala	114	36	30	45	199	100
SSC I contral.	103	6	30	> 180	106	80
SSC II contral.	75	14	20	100	116	20
SSC I ipsil.	88	20	45	150	160	30
SSC II ipsil.	73	32	45	80	141	60
Thalamus	124	39	30	80	184	60
Hypothalamus	124	22	60	100	189	80
SSC I contral.	133	14	20	> 180	125	60
SSC II contral.	124	20	30	> 180	182	20
SSC I ipsil.	158	16	30	150	189	30
SSC II ipsil.	156	24	10	120	227	20

Table 4.6 EFFECTS OF 30 mg/kg PENTOBARBITAL ON THE *MECHANICALLY* EVOKED POTENTIALS *(continued)*

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME AT WHICH THIS IS REACHED IN MINUTES	TIME AT WHICH A NON-SIGNIFICANT CHANGE IS BOT PRESENT ANYMORE	MAXIMUM PEAK LATENCY CHANGE IN MSEC	TIME AT WHICH THIS IS REACHED
N R G C	245	16	20	180	174	20
Thalamus	264	19	60	180	308	60
Amygdala	221	26	45	120	259	100
SSC I contral.	179	11	45	150	199	150
SSC II contral.	226	33	45	120	268	100
SSC I ipsil.	272	18	30	100	281	30
Thalamus	378	25	45	120	295	80
Hypothalamus	420	12	60	180	362	20
Amygdala	361	32	20	> 180	322	60
SSC I contral.	277	10	30	180	283	120
SSC II contral.	347	50	30	80	362	20
SSC II ipsil.	328	36	20	45	321	45

N.S. = Not Significant

For explanation: see Table 4.5.

Table 4.7. EFFECTS OF 15 mg/kg PENTOBARBITAL ON THE *ELECTRICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE		TIME AT WHICH THIS IS REACHED IN MINUTES	TIME AT WHICH A NON-SIGNIFICANT CHANGE IS NOT PRESENT ANYMORE	MAXIMUM PEAK LATENCY CHANGE IN MSEC	TIME AT WHICH THIS IS REACHED
SSC I contral.	20	103	N.S.			22	30
SSC II contral.	20	80	N.S.			22	20
SSC I contral.	24	59	N.S.	20		29	20
SSC II contral.	26	57	N.S.	20		34	30
SSC I contral.	31	60		5	20	38	20
SSC II contral.	34	32		20	30	48	30
SSC I ipsil.	36	66	N.S.			46	30
SSC II ipsil.	35	84	N.S.			54	45
N R G C	62	75	N.S.	20	30	83	20
Thalamus	57	46	N.S.	20		87	30
Hypothalamus	68	48		30	80	114	30
Amygdala	77	63		20	100	144	5
SSC I contral.	44	35		20	100	57	5
SSC II contral.	52	52		20	45	94	60
SSC I ipsil.	76	40		20	80	129	30
SSC II ipsil.	68	57		30	45	128	45
N R G C	115	52	N.S.	20	60	147	20
Thalamus	98	33		20	80	148	20
SSC I contral.	81	36		20	100	86	5
SSC II contral.	102	56	N.S.	30		170	60
SSC I ipsil.	120	50		20	60	165	30
SSC II ipsil.	125	40		45	60	196	30
Thalamus 1	32	28		30	100	180	60
Hypothalamus	122	68	N.S.	30	45	205	30
Amygdala	134	58	N.S.	30		219	30
SSC I contral.	127	65		20	30	134	20
SSC II contral.	148	48		20	30	193	30

Table 4.7. EFFECTS of 15 mg/kg PENTOBARBITAL ON THE *ELECTRICALLY* EVOKED POTENTIALS *(continued)*

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME AT WHICH THIS IS REACHED IN MINUTES	TIME AT WHICH A NON-SIGNIFICANT CHANGE IS NOT PRESENT ANYMORE	MAXIMUM PEAK LATENCY CHANGE IN MSEC	TIME AT WHICH THIS IS REACHED
N R G C	180	74 N.S.	30		242	20
Thalamus	181	43	30		289	20
Hypothalamus	175	62 N.S.	30		303	30
Amygdala	183	60 N.S.	45		290	30
SSC I contral.	182	25	20	80	187	20
SSC II contral.	208	73 N.S.			242	30
SSC I ipsil.	257	30	20	30	319	5
Thalamus	334	37	30	100	362	20
Hypothalamus	406	29	30	60	377	45
Amygdala	270	56 N.S.	45		364	30
SSC I contral.	374	17	30	100	386	5
SSC II contral.	335	64 N.S.	20		348	30
SSC I ipsil.	399	44	20	30	367	20
SSC II ipsil.	334	62 N.S.	45			
Thalamus	412	37	30	60	464	20
Amygdala	424	37	5	20	373	20

N.S. = Not Significant

For explanation: see Table 4.5.

Table 4.8. EFFECTS OF 15 mg/kg PENTOBARBITAL ON THE *MECHANICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME AT WHICH THIS IS REACHED IN MINUTES	TIME AT WHICH A NON-SIGNIFICANT CHANGE IS NOT PRESENT ANYMORE	MAXIMUM PEAK LATENCY CHANGE IN MSEC	TIME AT WHICH THIS IS REACHED
SSC I contral.	20	111 N.S.	20		25	20
SSC I contral.	25	80 N.S.	20		32	20
SSC I contral.	32	49 N.S.	20		40	20
SSC II contral.	29	80 N.S.	20		39	30
SSC I ipsil.	45	80 N.S.	10		97	20
SSC II ipsil.	35	53 N.S.	20		49	20
N R G C	88	34	45	120	151	80
Thalamus	74	32	30	45	139	20
Hypothalamus	67	48 N.S.	30		144	45
Amygdala	69	32	10	20	134	20
SSC I contral.	52	22	10	45	63	20
SSC II contral.	55	37	20	30	73	10
SSC I ipsil.	74	52	10	30	136	20
SSC II ipsil.	70	35	30	60	120	20
Thalamus	127	41	30	80	208	20
Hypothalamus	107	62 N.S.	20		224	45
Amygdala	133	39	10	20	197	20
SSC I contral.	101	16	20	120	141	20
SSC II contral.	80	85 N.S.	10		141	30
SSC II ipsil.	134	17	30	120	197	20
SSC I contral.	134	40	20	120	145	20
SSC II contral.	125	53 N.S.	20		199	30

Table 4.8. EFFECTS OF 15 mg/kg PENTOBARBITAL ON THE *MECHANICALLY* EVOKED POTENTIALS *(continued)*

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME AT WHICH THIS IS REACHED IN MINUTES	TIME AT WHICH A NON-SIGNIFICANT CHANGE IS NOT PRESENT ANYMORE	MAXIMUM PEAK LATENCY CHANGE IN MSEC	TIME AT WHICH THIS IS REACHED
N R G C	177	30	45	120	226	100
Thalamus	279	57 N.S.	30		334	60
Hypothalamus	184	54 N.S.	30		347	45
Amygdala	236	47 N.S.	20		300	20
SSC I contral.	229	40 N.S.	10		230	30
SSC I ipsil.	250	30	30	30	318	20
SSC II ipsil.	296	29	10	20	327	20
Hypothalamus	360	44 N.S.	10		351	20
Amygdala	356	23	20	120	397	20
SSC I contral.	286	27	20	120	288	20
SSC II contral.	312	73 N.S.	20		348	30

N.S. = Not Significant

For explanation: see Table 4.5.

Preanesthetic values were restored after 60-100 minutes. The SEP in the ipsilateral somatosensory cortex II followed the same pattern as that in the contralateral SSC II.

In table 4.6. the effects of the same dose of pentobarbital on the *mechanical* SEP are shown. With the exception of the first peak in the NRGC SEP and the second and third in the SEP of the ipsilateral SSC I the peaks with latency times below 70 msec were not significantly changed by this dose of pentobarbital.

The later waves in the NRGC SEP were reduced to 20% of their original amplitudes; after 180 minutes the amplitudes were no longer significantly different from the preanesthetic value.

The SEP of the thalamus showed successively a decrease in amplitude to 39%, 19% and 25%. After 80, 180 and 120 minutes respectively the reduction was no longer significant. The hypothalamus was strongly influenced by pentobarbital over a period of 60 minutes.

The amplitudes of the later waves in the SEP of the amygdala were 66% decreased, this effect lasting for 45 to even more than 180 minutes.

The 73-103 msec component of the cortical structures was reduced in amplitude to 6, 14, 20 and 32%, with return to the original value after 80-180 minutes. An even more remarked reduction was seen in the 124-158 msec wave; this lasted at least 120 minutes. The later waves were 90% decreased in the SSC I both contra- and ipsilateral, but only 50% to 66% reduction was seen in the SSC II contra- and ipsilateral.

Pentobarbital tended also with *mechanical* stimulation to prolong the latencies of the SEP for those peaks with an original latency of < 275 msec. This was about 5 msec for the early peaks to a maximum of 40 msec for the later waves.

Table 4.7. shows the effects of 15 mg/kg pentobarbital on the *electrically* evoked potentials. The early (<40 msec) waves were not significantly influenced, except for the 31-34 msec component in the contralateral cortex; this reduction lasted for only 20-30 minutes. For the waves with latencies between 50 and 150 msec the results were as follows: NRGC, not significantly influenced; thalamus, the first one not significantly reduced, the later two reduced to 33%; hypothalamus 68 msec peak 50% reduced and 122 msec peak not significantly influenced; amygdala the same; SSC I contralateral, reduced to 35, 36 and 65%; SSC II contralateral, reduced to 52(nonsignificant) and 48%; SSC I ipsilateral to 40 and 50% and SSC II ipsilateral to 57, 40

and 48%.

The next series of waves, 150-260 msec, were not significantly reduced except for the SSC I contra- and ipsilateral. The very late waves were not influenced in amygdala and SSC II and were reduced to 30-44% in thalamus, hypothalamus and ipsilateral cortex I, and to 17% in contralateral cortex I. The duration of the reduction did not exceed 100 minutes. The components with latencies to 260 msec were retarded in latency under the influence of pentobarbital.

The effects of 15 mg/kg pentobarbital on the *mechanically* evoked potentials are shown in table 4.8. Here only the components below 50 msec were not significantly changed. The later waves in the NRGC SEP were reduced to 34 and 30%; in the thalamus to 32, 41 and nonsignificantly; in the hypothalamus there was no significant change, in the amygdala there were reductions to 32, 29, 47 and 23%, in the SSC I contralateral to 22, 16, 40, 40 and 27%; in SSC II contralateral to 37 and nonsignificant; in SSC I ipsilateral to 52 and 30%; in SSC II ipsilateral to 35, 17 and 29%.

The significant reductions were maintained for nearly 120 minutes in some brain structures, but in most structures for a much shorter time, 45-60 minutes.

A shift in latency towards a longer duration was also seen for the waves with latencies shorter than 300 msec.

THIOPENTAL

The effect of 22.5 mg/kg of this short-acting barbiturate on the *electrically* evoked potentials is shown in table 4.9. The waves with peak latencies smaller than 50 msec were not significantly changed in most brain regions, while in the other areas the reduction lasted only a very short time

The later waves of the NRGC SEP were considerably decreased, to 25-12%; the reduction lasted 45-100 minutes. In the thalamus the reduction was approximately to 50%, the 65 msec and 121 msec component were not significantly influenced. The waves with the same latencies in the SEP of the hypothalamus also had their amplitudes 50% decreased, only the very late wave, 409 msec, being reduced to 25%. The amygdala had all its components 50% reduced; the last wave however, was nonsignificantly reduced. The reductions in all the subcortical structures never remained at their maxi-

Table 4.9. EFFECTS OF THIOPENTAL (22.5 mg/kg) ON THE *ELECTRICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE		TIME AT WHICH THIS IS REACHED IN MINUTES	TIME AT WHICH A NON-SIGNIFICANT CHANGE IS NOT PRESENT ANYMORE	MAXIMUM PEAK LATENCY CHANGE IN MSEC	TIME AT WHICH THIS IS REACHED
SSC I contral.	18	99	N.S.	3		20	5
SSC I contral.	23	69	N.S.	3		30	3
SSC I ipsil.	23	97	N.S.	30		30	5
SSC I contral.	27	78	N.S.	3		46	5
SSC II contral.	25	91	N.S.	3		40	10
N R G C	30	72		3	10	70	20
Thalamus	40	46	N.S.	20		59	3
Hypothalamus	39	36		5	30	70	3
SSC I contral.	42	25		3	10	53	5
SSC II contral.	36	53	N.S.	5		94	5
SSC I ipsil.	38	42		3	20	69	5
SSC II ipsil.	35	70		5	5	100	10
N R G C	60	25		3	45	109	20
Thalamus	65	55	N.S.	20		84	30
Hypothalamus	61	50	N.S.	5		116	10
Amygdala	69	41		5	10	97	10
SSC I contral.	66	7		3	30	82	60
SSC II contral.	54	31		5	30	137	10
SSC I ipsil.	61	43	N.S.	3		118	5
SSC II ipsil.	65	31		3	20		10
Thalamus	121	71	N.S.	20		191	30
Amygdala	123	46		5	10	185	10
SSC I contral.	95	18		5	20	120	30
SSC II contral.	118	24		5	20	164	3
SSC I ipsil.	100	13		5	30	208	5
SSC II ipsil.	152	38		5	45	203	10

Table 4.9. EFFECTS OF THIOPENTAL (22.5 mg/kg) ON THE *ELECTRICALLY* EVOKED POTENTIALS *(continued)*

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME AT WHICH THIS IS REACHED IN MINUTES	TIME AT WHICH A NON-CANT CHANGE IS NOT PRESENT ANYMORE	MAXIMUM PEAK LATENCY CHANGE IN MSEC	TIME AT WHICH THIS IS REACHED
N R G C	190	12	3	100	211	20
Thalamus	253	45	10	45	340	5
Hypothalamus	185	46	5	30	253	45
Amygdala	187	59	5	20	277	55
SSC I contral.	135	31	45	60	163	30
SSC II contral.	240	36	5	20	286	20
SSC I ipsil.	162	58 N.S.	5		253	20
SSC II ipsil.	313	25	5	20	327	5
Hypothalamus	409	25	20	80	338	5
Amygdala	223	56 N.S.	20		301	20
SSC I contral.	232	48 N.S.	10		246	30
SSC I ipsil.	368	24	20	60	394	5

N.S. = Not Significant

For explanation: see Table 4.5.

Table 4.10. EFFECTS OF THIOPENTAL (22.5 mg/kg) ON THE *MECHANICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME AT WHICH THIS IS REACHED IN MINUTES	TIME AT WHICH A NON-SIGNIFICANT CHANGE IS NOT PRESENT ANYMORE	MAXIMUM PEAK LATENCY CHANGE IN MSEC	TIME AT WHICH THIS IS REACHED
SSC I contral.	25	60 N.S.	10		35	10
SSC II contral.	25	86 N.S.	10		30	10
Amygdala	45	52 N.S.	30		84	30
SSC I contral.	36	71 N.S.	30		49	10
SSC II contral.	32	70 N.S.	10		46	30
SSC I ipsil.	37	72 N.S.	30		54	20
SSC II ipsil.	40	55 N.S.	45		63	45
N R G C	76	23	20	150	165	45
Thalamus	88	66 N.S.	20		144	10
Hypothalamus	63	36 N.S.	30		90	20
Amygdala	7	55 N.S.	15		173	20
SSC I contral.	58	37	45	80	68	20
SSC II contral.	58	44	10	20	83	10
SSC I ipsil.	71	58 N.S.	10		149	60
SSC II ipsil.	68	40	10	80	132	20
Thalamus	149	70 N.S.	20		185	20
Hypothalamus	108	43 N.S.	30		164	20
SSC I contral.	107	38	20	80	113	20
SSC II contral.	120	51	10	20	168	45
SSC I ipsil.	108	30	20	80	195	45
SSC II ipsil.	173	20	20	80	280	20

Table 4.10. EFFECTS OF THIOPENTAL (22.5 mg/kg) ON THE *MECHANICALLY* EVOKED POTENTIALS *(continued)*

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME AT WHICH THIS IS REACHED IN MINUTES	TIME AT WHICH A NON-SIGNIFICANT CHANGE IS NOT PRESENT ANYMORE	MAXIMUM PEAK LATENCY CHANGE IN MSEC	TIME AT WHICH THIS IS REACHED
N R G C	205	28	20	80	309	60
Hypothalamus	227	22	30	80	320	20
Amygdala	193	21	10	20	224	20
SSC I contral.	154	29	20	45	272	30
SSC II contral.	249	68 N.S.	10		270	30
SSC I ipsil.	160	23	10	20	247	20
Thalamus	331	45	20	45	365	20
Hypothalamus	401	26	30	120	374	30
Amygdala	347	33	15	20	360	20
SSC I contral.	292	14	45	120	268	10
SSC II ipsil.	334	18	30	80	387	20
SSC I ipsil	343	37	10	20	360	20

N.S. = Not Significant

For explanation: see Table 4.5.

Table 4.11. EFFECTS OF THIOPENTAL (15 mg/kg) ON THE *ELECTRICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME AT WHICH THIS IS REACHED IN MINUTES	TIME AT WHICH A NON-SIGNIFICANT CHANGE IS NOT PRESENT ANYMORE	MAXIMUM PEAK LATENCY CHANGE IN MSEC	TIME AT WHICH THIS IS REACHED
SSC I contral.	18	80 N.S.	5		20	30
SSC II contral.	20	71 N.S.	3		23	3
SSC I contral.	22	80 N.S.	5		31	10
SSC II contral.	25	73 N.S.	3		36	3
SSC I ipsil.	25	89 N.S.	5		34	10
N R G C	33	75 N.S.	5		50	5
Thalamus	42	57 N.S.	5		56	30
Hypothalamus	44	37	3	5	62	5
SSC I contral.	30	31	3	5	47	10
SSC II contral.	32	45 N.S.	3		55	5
SSC I ipsil.	34	61 N.S.	3		57	5
SSC II ipsil.	33	75 N.S.	5		45	3
N R G C	66	54	5	30	96	5
Thalamus	64	76 N.S.	5		97	30
Hypothalamus	74	62 N.S.	10		111	20
Amygdala	71	74 N.S.	5		139	10
SSC I contral.	68	68 N.S.	3		93	10
SSC II contral.	51	68 N.S.	3		89	5
SSC I ipsil.	60	40 N.S.	10		93	5
SSC II ipsil.	72	57 N.S.	5		113	10
N R G C	123	60	5	30	169	5
Thalamus	105	69 N.S.	20		153	5
Hypothalamus	105	23	5	20	159	20
Amygdala	135	41	5	10	205	20
SSC I contral.	101	21	5	80	136	10
SSC II contral.	120	24	3	20	156	5
SSC I ipsil.	108	54 N.S.	10		160	3
SSC II ipsil.	147	30	20	60	204	10

Table 4.11. EFFECTS OF THIOPENTAL (15 mg/kg) ON THE *ELECTRICALLY* EVOKED POTENTIALS *(continued)*

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME AT WHICH THIS IS REACHED IN MINUTES	TIME AT WHICH A NON-SIGNIFICANT CHANGE IS NOT PRESENT ANYMORE	MAXIMUM PEAK LATENCY CHANGE IN MSEC	TIME AT WHICH THIS IS REACHED
N R G C	253	24	5	30	321	20
Thalamus	160	102 N.S.	20		197	5
Hypothalamus	181	35	20	60	245	20
Amygdala	228	63 N.S.	10		322	20
SSC I contral.	145	57	10	30	180	3
SSC II contral.	194	46	5	60	229	5
SSCI ipsil.	170	51 N.S.	3		222	3
SSC II ipsil.	347	15	20	45	378	10
Thalamus	315	44	5	30	357	5
Hypothalamus	376	70 N.S.	10		401	10
Amygdala	395	74 N.S.	10		417	20
SSC I contral.	257	38 N.S.	5		280	5
SSC II contral.	267	40 N.S.	5		293	20
SSC I ipsil.	339	48 N.S.	5		382	5

N.S. = Not Significant

For explanation: see Table 4.5.

Table 4.12. EFFECTS OF THIOPENTAL (15 mg/kg) ON THE *MECHANICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...	PERCENTAGE	TIME AT WHICH THIS IS REACHED IN MINUTES	TIME AT WHICH A NON-SIGNIFICANT CHANGE IS NOT PRESENT ANYMORE	MAXIMUM PEAK LATENCY CHANGE IN MSEC	TIME AT WHICH THIS IS REACHED
SSC I contral.	24	75	N.S.	5		33	5
N R G C	30	62	N.S.	20		35	20
Thalamus	49	48	N.S.	20		60	20
Hypothalamus	44	43	N.S.	20		54	45
SSC I contral.	30	55	N.S.	5		40	20
SSC II contral.	31	54	N.S.	20		35	60
SSC I ipsil.	43	59	N.S.	20		40	20
SSC II ipsil.	45	47	N.S.	20		51	10
N R G C	68	16		30	> 120	76	30
Thalamus	66	67	N.S.	20		96	30
Hypothalamus	73	66	N.S.	45		122	45
Amygdala	82	55	N.S.	20		131	20
SSC I contral.	60	103	N.S.	20		94	20
SSC II contral.	70	55	N.S.	45		93	30
SSC I ipsil.	64	54	N.S.	20		73	20
SSC II ipsil.	71	36	N.S.	20		72	30
N R G C	91	40		30	80	130	20
Thalamus	114	66	N.S.	20		164	20
Hypothalamus	132	62	N.S.	20		235	45
Amygdala	167	22		20	30	244	20
SSC I contral.	107	32	N.S.	20		150	30
SSC II contral.	110	38		20	30	137	30
SSC I ipsil.	109	25		20	45	125	20
SSC II ipsil.	134	29		30	30	145	30

Table 4.12. EFFECTS OF THIOPENTAL (15 mg/kg) ON THE *MECHANICALLY* EVOKED POTENTIALS *(continued)*

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME AT WHICH THIS IS REACHED IN MINUTES	TIME AT WHICH A NON-SIGNIFICANT CHANGE IS NOT PRESENT ANYMORE	MAXIMUM PEAK LATENCY CHANGE IN MSEC	TIME AT WHICH THIS IS REACHED
N R G C	185	36	20	45	218	10
Thalamus	261	34	20	30	327	20
Hypothalamus	316	36	45	80	365	45
Amygdala	306	23	20	80	283	30
SSC I contral.	184	29	30	80	229	30
SSC II contral.	170	70 N.S.	20		202	60
SSC I ipsil.	195	19	20	60	235	20
SSC II ipsil.	257	41 N.S.	30		285	10
N R G C	292	40	20	> 120	352	45
SSC II contral.	279	30	30	45	288	30
SSC I ipsil.	329	34	30	60	361	20

N.S. = Not Significant

For explanation: see Table 4.5.

mum for longer than 45 minutes. Of the cortical regions the sensory cortex I contralateral was the most influenced by thiopental; the 66 msec peak ecreased to 7%, the 75 msec peak to 18%, the 135 msec peak to 35% and the 232 msec peak nonsignificantly to 48%. In the sensory cortex II contralateral there was also a smaller reduction in amplitude as the peak latencies increased to 31, 24 and 36%, the effect being nonsignificantly changed in the 61 peak of the SEP; a very marked reduction was seen in the 100 msec peak, to 13%, a nonsignificant reduction in the 162 msec peak and reduction to 24% in the very late, 368 msec, peak. In the sensory cortex II ipsilateral the SEP components 50 msec were 62-75% reduced. The time at which the amplitude no longer significantly differed from the preanesthetic values was 10 minutes for the slightly reduced waves, 20-30 minutes for the moderately reduced waves and 45 minutes for the strongly reduced ones. In the very late wave, in the contralateral SSC I, however, the reduction lasted much longer.

There was also a change in latencies occurring very quickly in the early waves and somewhat more slowly in the later waves.

The same dose of thiopental was also without effect on the early (< 50 msec) waves in the needle-prick-evoked potential (Table 4.10.). The later waves in this SEP of NRGC were reduced to a quarter. In the thalamus the 66 and 149 msec potential were not significantly changed while the 331 msec one was reduced to 50%. In the *mechanically* evoked potential of the hypothalamus 22.5 mg/kg thiopental did not significantly change the components between 60-150 msec; the later waves were reduced to 25%. In the amygdala the 87 msec component was not significantly changed, the 193 msec peak was reduced to 21% and the late wave to 53%. In the somatosensory cortex I contralateral the 50-150 components were reduced to 29 and 14%. The contralateral cortex II had a reduction to 44-68%, with a nonsignificant effect in the last component. In the ipsilateral SSC I the 71 msec wave was not significantly changed; the waves later than 100 msec were reduced about 70%. The ipsilateral cortex II showed a reduction to 40% for the 68 msec peak and to 20% for the later waves. The maximum reduction in all brain structures was reached within 45 minutes and the amplitudes had returned to preanesthetic levels in 20 minutes for the 50% reduced waves, in 45-80 minutes for the 66% reduced waves and in sometimes as much as 120 minutes for the 80% reduced waves. A prolon-

gation of the latency times was observed; this was greatest in the medium-latency waves.

In another serie of experiments the effect of 66% of the above mentioned dose, i.e. 15 mg/kg, was tested. Table 4.11. shows the effects of this dose of thiopental on the *electrically* evoked potentials. The early components, < 50 msec, were not significantly changed, or were affected for a very short time, (5 minutes).

In the nucleus reticularis gigantocellularis the components between 50 and 150 msec were reduced to 54-60% and the last component to 24%. In the thalamus no significant change was seen except for the very late wave (about 56% reduction). The 74 and 376 msec peaks in the SEP of the hypothalamus were not significantly changed while the two waves in between were reduced to 23 and 35%. The amygdala SEP was not significantly changed except for the 136 msec peak. In the contralateral cortex I the first peak with a latency of > 50 msec and the last peak were not significantly reduced in the 51 msec peak and the very late wave (267 msec). The two peaks in between were reduced to 24 and 46%. The waves with peak latencies > 50 msec were not significantly reduced in the ipsilateral cortex I.

In the ipsilateral cortex II the 72 msec peak of the SEP was not significantly changed and the two later ones were reduced to 30 and 15% respectively. The maximum reduction in all brain structures was reached within 20 minutes and for the strongly reduced centers was maintained even up to 80 minutes.

The latency times were also prolonged under the action of thiopental. The maximum effect was reached within 20 minutes.

Table 4.12. shows the *mechanical* SEP and the effects of 15 mg/kg thiopental on these potentials. Again the components < 50 msec were not significantly changed, the later components gave the following results: NRGC reduced to 16-40%, thalamus reduced nonsignificantly and to 36%; amygdala nonsignificantly reduced, 22 and 23%; contralateral cortex I nonsignificantly and 29%; contralateral somatosensory cortex II nonsignificantly to 38% and nonsignificantly to 30%; the ipsilateral cortex I nonsignificantly and to 25, 19 and 34% and the ipsilateral cortex II nonsignificantly, to 39% and nonsignificantly.

The maximum reduction was reached within 45 minutes and lasted for up

to 120 minutes in the NRGC and 80 minutes in contralateral cortex II.

A latency shift was also seen, amounting to 6-49 msec in the 50-100 msec waves, and 30-45 msec in the 16-103 msec waves; in the medium latency waves the last waves were sometimes lengthened but some were shortened.

4.4.3. Discussion and conclusion

The early components with latencies between 10 and 50 msec were not significantly changed in most brain structures. Where a significant reduction was seen this reduction lasted only for a few minutes. This is in agreement with others (CLARK and ROSNER 1973; ANGEL et al. 1973; BAUST et al. 1977; ALLISON et al. 1963).

Different effects were seen in the 50-150 msec components, evoked by Aδ fiber stimulation, and in the 150-280 msec components (C fiber evoked potential) and later components in different brain structures with different barbiturate doses.

Electrically evoked potentials in NRGC between 50-150 msec were reduced to 25-48% by the highest dose and nonsignificantly by low doses of pentobarbital; the reduction was only to 54-60% with the low dose of thiopental. The amplitudes of the later components in this region were decreased to 12-17% in the high-dose experiments, to 24% with low-dose thiopental and nonsignificantly with low-dose pentobarbital. The *needle-prick* evoked potential was even more reduced in the NRGC under barbiturate anesthesia; in all other components > 50 msec there was a reduction to between 16 and 40%.

The 50-150 msec components in the evoked potentials of the thalamus were not significantly changed, either in *electrical* or in *mechanical* stimulation, after the high and low doses of thiopental. Pentobarbital, both low and high doses, did cause the *electrically* evoked potentials in this region decrease to 28-46%; the *mechanically* evoked potential was less reduced, to 32-60%.

The later waves in the thalamus evoked potential were not significantly changed by the low pentobarbital and thiopental doses after *electrical* stimulation; *mechanically* evoked potentials were significantly reduced by low-dose thiopental.

High-dose pentobarbital reduced the C fiber evoked potential to 15-20%, but high-dose thiopental only to 45% for both *electrically* and

mechanically evoked potentials. The very late wave in the SEP in this region was quite considerably reduced, to less than 45%. A similar result was found by SATOH (1980) in cats.

The effects of barbiturates on the hypothalamus were even less marked. The 50-150 msec components were nonsignificantly reduced. The *electrical* C fiber potential was nonsignificantly decreased by pentobarbital even in high dosage. It was reduced to 46% by the high dose of thiopental and to 35% by the low dose of thiopental. The *mechanical* C fiber potential was reduced to 12% by the high dose of pentobarbital and nonsignificantly by the low dose of pentobarbital.

In the amygdala the hogh dose of pentobarbital flattened both the *electrically* and *mechanically* evoked potentials to 12-39%. The low dose of pentobarbital reduced the C fiber potential significantly, while the *electrical* Aδ fiber potential was nonsignificantly reduced to 63%; the *mechanical* response was reduced to 32-39%. The Aδ fiber response - the first one - was not significantly changed by eitehr dose of thiopental; the second C fiber wave, if present, was reduced to 45% with *electrical* and 22% with *mechanical* stimulation.

Besides the NRGC the contralateral cortex seems to be the most influenced by pentobarbital: the high dose reduced Aδ and C fiber potentials to 10-5% and the low dose to 30 and 40% respectively. The high dose of thiopental reduced the Aδ fiber potential to 7-40% and the C fiber potential to 30%, and the low dose of thiopental reduced Aδ fiber potential nonsignificantly and C fiber to 30-50%. These reductions were also found by ANGEL et al. (1973) in rats and rabbits, by PIMMEL et al. (1976) in rhesus monkeys and by CLARK and ROSNER (1973) and BAUST et al. (1977) and ALLISON et al. (1963) in human subjects.

In all these species the reduction in amplitude of the late waves was related to the dose of barbiturate.

The contralateral sensory cortex II, on the other hand, seems to be less sensitive to barbiturates. No significant change was found in the C fiber evoked potential, except with the high dose of pentobarbital; in this case a 50% reduction was seen. The Aδ fiber potential seemed to be more influenced, being reduced to 14-30% by the high dose of pentobarbital, to 24-50% by the high dose of thiopental, and to 37% to nonsignificant with the low dose of thiopental.

The ipsilateral cortex I reacted intermediately, the Aδ fiber potential was decreased to 16-48% with high dose pentobarbital and to 40-52% with low dose pentobarbital, while with thiopental the first peak of this component was not significantly changed and the second one was reduced maximally to 13%. The *electrically* evoked C fiber potential was also not significantly changed by thiopental, while the *mechanical* response was reduced to 20% in both the high and low dose experiments. Pentobarbital reduced this component to 43% or higher.

The ipsilateral cortex II was slightly more affected than the contralateral site; the reduction was to 19-57%. The high dose of pentobarbital reduced the *electrically* evoked Aδ and C fiber potentials significantly. The low dose of pentobarbital reduced only the *mechanically* evoked Aδ and C fiber potentials. Both high and low doses of thiopental reduced significantly the *mechanically* evoked Aδ fiber and the *electrically* and *mechanically* evoked Aδ and C fiber potential.

The increase in latency has also been found in rats and rabbits (ANGEL et al. 1973) and man (ALLISON et al. 1963; BAUST et al. 1977; CLARK and ROSNER 1973) after administration of a barbiturate.

Barbiturates act mainly on the NRGC and the cortex. The hypothalamus, thalamus and amygdala are only slightly influenced. A difference is also seen between the cortical regions. The sensory cortex I seems to be the most influenced and the sensory cortex II the least. There is also a tendency for the Aδ fiber potential to decrease more than the C fiber potential.

Pentobarbital 15 mg/kg is not a suitable anesthetic for painful surgery. A dose of twice as much as this, however, seems to give significant pain relief for about one hour. Thiopental cannot be used as a single anesthetic for surgery unless this is completed within 5 minutes.

4.5. Effects of ketamine on the SEP

4.5.1. Introduction

Ketamine, a relatively new phencyclidine analog, was introduced for anesthesia in children and is nowadays frequently used for experimental work in rodents, carnivores, ruminants and primates. It depresses the central nervous system, the depth of depression depending on the dose given. It produces catalepsy, a state in which the body remains passively in any position in which it has been placed. It has minor effects on respiration and circulation. In man it has hallucinogenic effects; in animals it often induces nystagmus. It has an analgesic action, but a strong muscle tone remains. In this chapter the effects of three doses of ketamine on the noxious *electrically* and *mechanically* evoked potentials are discussed. The doses were 15 mg/kg, 10 mg/kg and 5 mg/kg of ketamine (as hydrochloride) intravenously.

4.5.2. Results

The maximum decrease in amplitude, the significance of this reduction ($p < 0.01$), the time at which this maximum was reached, the time in minutes at which the reduction was no longer significant, the maximum change in latency time and the time in minutes at which this change was reached are given.

In table 4.13. these figures represent the effects of a large dose of ketamine HCl (15 mg/kg i.v.) on the *electrically* evoked potential. The peaks with latencies smaller than 45 msec were not significantly reduced; there was a small increase in latency, about 0-8 msec. The maximum effect was reached within 45 minutes.

The later components in the SEP of the N R G C were reduced to 30-41%. This maximum reduction was reached within 10 minutes and was maintained until 30-45 minutes after ketamine administration.

In the thalamus the 65 msec peak was decreased to 36%, the 203 msec peak to 26% and the very late component to 6%. This maximum persisted after 5 and 30 minutes respectively and the reduction of the amplitudes lasted for 30-60 minutes. In the hypothalamus the change in amplitudes of the late waves was almost identical. Only the very late wave in the

Table 4.13. EFFECTS OF KETAMINE (15 mg/kg) ON THE *ELECTRICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-AN.E STHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
SSC I contral.	18	71 N.S.	20		15	20
SSC I contral.	23	76 N.S.	5		21	20
SSC II contral.	31	70 N.S.	10		36	30
SSC I ipsil.	23	70 N.S.	10		28	10
N R G C	33	89 N.S.	20		40	5
Thalamus	44	43 N.S.	5		50	5
Hypothalamus	42	56 N.S.	20		50	10
SSC I contral.	28	68 N.S.	5		30	45
SSC II contral.	40	85 N.S.	10		44	30
SSC I ipsil.	42	63 N.S.	5		50	10
N R G C	65	30	5	80	73	10
Thalamus	65	36	5	30	83	5
Hypothalamus	67	34	10	45	84	5
Amygdala	59	28	10	20	103	5
SSC I contral.	48	48	5	20	50	20
SSC II contral.	55	40	5	30	62	30
SSC I ipsil.	72	50	5	20	91	30
SSC II ipsil.	72	25	5	20	104	20
Amygdala	111	26	5	60	186	5
SSC I contral.	104	26	10	45	107	30
SSC II contral.	108	22	5	45	86	5
N R G C	143	41	10	30	179	5
Thalamus	203	26	30	60	302	20
Hypothalamus	235	27	30	60	205	5
Amygdala	170	25	20	60	280	5
SSC II contral.	156	19	20	60	127	10
SSC I ipsil.	156	41	5	30	139	5
SSC II ipsil.	137	10	5	45	186	20

Table 4.13. EFFECTS OF KETAMINE (15 mg/kg) ON THE *ELECTRICALLY* EVOKED POTENTIALS *(continued)*

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-AN ESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
N R G C	365	39	10	45	297	20
Thalamus	353	6	30	6	383	10
Hypothalamus	402	30	60	120	382	10
Amygdala	389	18	20	60	401	5
SSC I contral.	267	18	45	120	256	10
SSC II contral.	277	9	30	120	241	10
SSC I ipsil.	336	16	30	100	305	5
SSC II ipsil.	317	7	30	45	294	5

N.S. = Not Significant

Vertically the potentials with the same latency times (mean of six dogs) present in different brain regions are grouped together.
Horizontally the maximum reduction in amplitude (mean of six dogs), the time at which this maximum is present (mean of six dogs), the time at which the reduction is no longer significant, the maximum change in latency time (mean of six dogs) and the time at which this maximum is present (mean of six dogs), are shown.

Table 4.14. EFFECTS OF KETAMINE (15 mg/kg) ON THE *MECHANICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
SSC I contral.	23	81 N.S.	10		24	20
N R G C	38	45	20	60	42	20
Thalamus	48	48 N.S.	20		60	30
Hypothalamus	45	37	30	45	59	20
SSC I contral.	33	89 N.S.	20		32	20
SSC II contral.	34	63 N.S.	20		45	20
SSC I ipsil.	44	46 N.S.	20		48	30
SSC II ipsil.	37	20	20	45	43	20
N R G C	79	25	20	80	110	20
Thalamus	97	46	20	80	124	20
Hypothalamus	72	45	20	45	100	45
Amygdala	89	31	30	100	121	20
SSC I contral.	60	33	10	20	66	20
SSC II contral.	61	42	10	20	73	10
SSC I ipsil.	68	15	20	80	74	30
SSC II ipsil.	73	32	30	60	110	20
Hypothalamus	129	17	30	45	170	20
Amygdala	135	44	20	80	198	20
SSC I contral.	101	30	20	60	97	20
SSC II contral.	123	29	20	45	164	30
N R G C	154	21	30	80	192	45
Thalamus	168	41	20	30	200	20
Hypothalamus	220	14	30	80	276	30
Amygdala	204	10	20	45	257	20
SSC I contral.	144	34	30	45	144	20
SSC I ipsil.	161	15	20	80	192	20
SSC II ipsil.	166	7	30	100	208	45

Table 4.14. EFFECTS OF KETAMINE (15 mg/kg) ON THE *MECHANICALLY* EVOKED POTENTIALS *(continued)*

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
N R G C	317	30	20	60	340	20
Thalamus	343	45	20	45	357	20
Amygdala	410	12	30	45	391	30
SSC I contral.	267	23	30	45	265	20
SSC II contral.	269	19	20	45	218	30
SSC I ipsil	256	22	20	60	290	30
SSC II ipsil.	331	10	30	80	336	20

N.S. = Not Significant

For explanation: see Table 4.13.

Table 4.15. EFFECTS OF KETAMINE (10 mg/kg) ON THE *ELECTRICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
SSC I contral.	17	94 N.S.	30		18	20
SSC I contral.	22	88 N.S.	5		33	20
SSC II contral.	22	52 N.S.	5		11	10
SSC I ipsil.	25	76 N.S.	5		21	5
SSC I contral.	28	64 N.S.	10		30	20
N R G C	34	85 N.S.	5		39	30
Thalamus	41	50 N.S.	10		45	20
Hypothalamus	39	53 N.S.	20		53	20
Amygdala	32	60 N.S.	20		54	20
SSC I contral.	36	55 N.S.	10		41	10
SSC II contral.	36	75 N.S.	10		39	20
SSC I ipsil.	34	69 N.S.	5		38	30
SSC II ipsil.	32	40 N.S.	5		38	10
N R G C	85	42	10	60	105	10
Thalamus	65	37	20	120	93	5
Hypothalamus	72	39	20	45	87	30
Amygdala	69	38	20	60	131	20
SSC I contral.	48	48	20	30	53	20
SSC II contral.	51	27	5	30	57	20
SSC I ipsil.	65	64	5	30	131	10
SSC II ipsil.	56	29	10	20	62	5
N R G C	131	44	10	30	164	5
Thalamus	116	29	5	60	157	20
Amygdala	143	17	20	60	169	5
SSC I contral.	95	18	10	45	106	10
SSC II contral.	126	18	10	45	99	10
SSC I ipsil.	139	36	10	20	174	10
SSC II ipsil.	145	17	10	20	172	20

Table 4.15. EFFECTS OF KETAMINE (10 mg/kg) ON THE *ELECTRICALLY* EVOKED POTENTIALS *(continued)*

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
N R G C	205	29	5	20	254	10
Thalamus	353	18	30	60	382	20
Hypothalamus	226	28	30	60	240	10
Amygdala	199	32	30	45	210	5
SSC I contral.	203	28	20	45	213	10
SSC II contral.	202	30	10	20	146	5
SSC I ipsil.	240	20	10	20	249	5
SSC II ipsil.	305	24	30	45	325	45
Hypothalamus	402	29	10	120	349	20
Amygdala	404	24	20	60	361	45
SSC I contral.	309	15	20	45	313	10
SSC II contral.	315	9	30	120	247	5

N.S. = Not Significant

For explanation: see Table 4.13.

Table 4.16. EFFECTS OF KETAMINE (10 mg/kg) ON THE *MECHANICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
SSC I contral.	24	70 N.S.	5		25	30
SSC II contral.	27	58 N.S.	20		28	20
Thalamus	40	53 N.S.	10		51	20
Hypothalamus	45	61 N.S.	20		53	20
SSC I contral.	30	71 N.S.	20		31	30
SSC II contral.	37	51 N.S.	20		46	45
SSC I ipsil.	66	39 N.S.	20		78	30
N R G C	88	37	20	60	108	20
Thalamus	70	37	10	80	82	20
Hypothalamus	69	46	10	20	98	30
Amygdala	92	36	30	60	131	20
SSC I contral.	65	58	10	30	67	20
SSC II contral.	61	60	10	20	57	20
SSC I ipsil.	82	21	20	45	92	30
SSC II ipsil.	72	30	20	45	87	20
Thalamus	129	42	10	30	166	30
Hypothalamus	110	31	20	45	155	30
Amygdala	159	30	20	80	186	45
SSC I contral.	135	30	30	45	135	30
SSC II contral.	80	24	10	45	90	30
SSC I ipsil.	164	12	20	45	141	20
SSC II ipsil.	170	9	20	60	149	30

Table 4.16. EFFECTS OF KETAMINE (10 mg/kg) ON THE *MECHANICALLY* EVOKED POTENTIALS *(continued)*

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
N R G C	227	11	20	30	250	20
Thalamus	288	40	20	45	358	30
Hypothalamus	179	20	20	80	215	30
Amygdala	261	14	30	45	285	45
SSC I contral.	257	22	20	45	269	45
SSC II contral.	167	24	20	45	151	20
SSC I ipsil.	273	14	20	60	233	20
SSC II ipsil.	326	19	30	60	302	20
Hypothalamus	387	7	30	60	396	20
SSC II contral.	337	21	20	45	252	20

N.S. = Not Significant

For explanation: see Table 4.13.

Table 4.17. EFFECTS OF KETAMINE (5 mg/kg) ON THE *ELECTRICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
SSC I contral.	22	72 N.S.	5		20	5
SSC II contral.	21	80 N.S.	5		20	5
SSC I contral.	28	71 N.S.	5		26	5
N R G C	36	75 N.S.	5		50	20
Thalamus	40	45 N.S.	5		41	5
Hypothalamus	41	60 N.S.	5		49	30
SSC I contral.	44	62 N.S.	5		42	5
SSC II contral.	35	83 N.S.	5		39	5
SSC II ipsil.	37	63 N.S.	5		44	5
Thalamus	61	54	5	10	64	10
Hypothalamus	66	60 N.S.	20		79	30
Amygdala	64	51 N.S.	5		83	5
SSC I contral.	61	54 N.S.	5		62	5
SSC II contral.	55	46	5	10	60	5
SSC I ipsil.	68	70 N.S.	10		68	10
SSC II ipsil.	73	66 N.S.	5		87	5
N R G C	91	56	5	10	96	5
Thalamus	100	53 N.S.	5		119	5
Hypothalamus	128	47	5	10	190	10
Amygdala	108	40 N.S.	5		155	5
SSC I contral.	86	44 N.S.	10		95	10
SSC II contral.	103	59 N.S.	5		117	10
SSC I ipsil.	104	75 N.S.	10		125	10
SSC II ipsil.	123	64 N.S.	5		146	5

Table 4.17. EFFECTS OF KETAMINE (5 mg/kg) ON THE *ELECTRICALLY* EVOKED POTENTIALS *(continued)*

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
N R G C	221	41	5	45	208	5
Thalamus	227	39	10	20	250	20
Hypothalamus	223	31	20	30	336	5
Amygdala	178	43	5	20	253	20
SSC I contral.	185	20	10	20	191	10
SSC II contral.	252	27	10	20	223	10
SSC I ipsil.	189	47	5	10	179	10
SSC II ipsil.	280	41	20	30	323	10
Thalamus	409	24	20	30	421	5
Amygdala	327	40	10	20	411	20
SSC I contral.	321	37	20	45	326	10
SSC I ipsil.	304	21	20	30	237	20

N.S. = Not Significant

For explanation: see Table 4.13.

Table 4.18. EFFECTS OF KETAMINE (5 mg/kg) ON THE *MECHANICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
SSC I contral.	18	64 N.S.	20		20	20
SSC I contral.	24	86 N.S.	20		25	30
SSC II contral.	25	88 N.S.	20		25	20
SSC I contral.	34	103 N.S.	20		34	20
SSC II contral.	35	81 N.S.	20		31	20
SSC I contral.	44	102 N.S.	20		44	20
SSC I ipsil.	41	87 N.S.	30		53	20
SSC II ipsil.	47	80 N.S.	20		44	30
N R G C	93	47	5	10	116	30
Thalamus	69	64	5	10	85	5
Hypothalamus	61	97 N.S.	10		71	20
Amygdala	70	90 N.S.	20		95	20
SSC I contral.	55	89 N.S.	20		59	20
SSC II contral.	62	166 N.S.	20		73	30
SSC I ipsil	66	82 N.S.	20		82	30
SSC II ipsil.	69	101 N.S.	20		85	20
N R G C	157	35	5	10	206	5
Thalamus	144	32	5	20	172	20
Hypothalamus	96	76 N.S.	20		130	20
Amygdala	147	70 N.S.	20		196	20
SSC I contral.	127	86 N.S.	20		150	20
SSC II contral.	133	65	10	20	152	30
SSC I ipsil.	163	47	20	30	173	45
SSC II ipsil.	160	54	10	20	138	30

Table 4.18. EFFECTS OF KETAMINE (5 mg/kg) ON THE *MECHANICALLY* EVOKED POTENTIALS *(continued)*

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
N R G C	235	25	20	30	340	20
Thalamus	354	35	20	30	335	20
Hypothalamus	179	61 N.S.	20		244	20
Amygdala	261	44	20	45	311	20
SSC I contral.	262	42	30	45	264	20
SSC II contral.	280	51	10	20	225	20
SSC I ipsil.	255	63	20	45	269	45
SSC II ipsil.	308	31	20	45	282	30
Hypothalamus	245	38	20	30	311	20

N.S. = Not Significant

For explanation: see Table 4.13.

hypothalamus was less reduced, but the reduction remained much longer. The same picture was seen in the amygdala.

In the contralateral cortex I and II a growing reduction occurred in the later waves, to 48, 26 and 18%, and the decrease lasted 20, 45 and more than 120 minutes. The reduction in amplitudes seen in the ipsilateral sensory cortex I was comparable with that in the contralateral cortex, to 50, 41 and 16%. The reduction in the ipsilateral cortex II was twice as great, to 25, 10 and 7%. The peaks with latency times between 48 and 72 msec were increased by not more than 2-44 msec in latency after ketamine injection. The later peaks had their latency sometimes increased and sometimes decreased. All changes in latency appeared within 45 minutes.

The same dose of ketamine influenced the *mechanically* evoked potential as shown in table 4.14. The components within 50 msec after the beginning of stimulation were not significantly changed, except for the NRGC and the hypothalamus where a 60% reduction in amplitude occurred. The later peaks were decreased to 21-30% in N R G C this effect lasting for 60-80 minutes.

In the thalamus these components were reduced to about 41-46% and the reduction remained significant for 30-80 minutes. The hypothalamus SEP was decreased to 45% for the components below 100 msec and to 15% for the later ones; a significant reduction persisted for 45-80 minutes. A 56-96% reduction occurred in the amygdala SEP components below 150 msec, while in the later waves the reduction was about 90%. This reduction lasted for 45-80 minutes. The later components in the SEP of the contralateral sensory cortex I had about 30% of their preanesthetic amplitudes; after 20-45 minutes the change was no longer significant. The 61 msec wave in the SEP of the contralateral sensory cortex II was reduced to 42% and the later ones to 29% and 19% for a period of 45 minutes. In the ipsilateral cortex I there was a reduction to 15-20% for 60-80 minutes and in the ipsilateral cortex II there were reductions to 32%, 7% and 10% lasting for 60-100 minutes. The latency times of all the peaks between 50 and 100 msec were increased by 6-33 msec. The latency times of the later peaks remained practically unchanged, with some tendency to increase but by not more than 65 msec.

Tables 4.15. and 4.16. show the effects of 10 mg/kg of ketamine on

the *electrically* and *mechanically* evoked potentials respectively. With both methods of stimulation the components shorter than 50 msec underwent no significant change in amplitude.

Returning to the later waves of the *electrically* evoked potential as shown in table 4.15. we see that in the N R G C the later components were reduced to 42-29%, while the preanesthetic level was restored within 20-60 minutes. The later waves of the SEP in the thalamus decreased in amplitude to 37, 29 and 18%; after 60-120 minutes the decrease was no longer significant. A similar decrease in amplitude occurred in the SEP of the hypothalamus; this lasted for only 45-60 minutes. In the amygdala the later waves of the SEP were reduced in amplitude to 38, 17, 32 and 24% and a significant effect was maintained for 40-60 minutes. In the SEP of the contralateral cortex I the amplitudes were reduced to 48, 18, 28 and 15% and returned to their preanesthetic levels within 45 minutes. In the SEP of the contralateral cortex II the effect was more marked, comprising reductions to 27, 18, 30 and 9% with a duration of 20-120 minutes. In the ipsilateral cortex I the reductions were to 64, 36 and 20% and lasted for 20-30 minutes. In the ipsilateral cortex II the later waves of the SEP showed reductions to 29, 17 and 24% lasting for 45 minutes.

The latencies of the peaks between 50 and 100 msec were increased by 6-62 msec, while the later peaks also had the same or longer latencies under ketamine anesthesia.

10 mg/kg ketamine (table 4.16.) had the following effect on the late waves (> 50 msec) of the *mechanically* evoked potential. The NRGC SEP was reduced to 37 and 11%, a reduction which lasted for 30-60 minutes; the thalamus SEP to 37, 42 and 40%, maintained for at least 80 minutes. In the hypothalamus these waves were reduced to 46, 31, 20 and 2%, this effect also lasting at least 30 minutes. The same reduction was seen in the amygdala. The contralateral cortex I showed reductions to 58, 30 and 22%, the initial value being restored within 45 minutes. The contralateral cortex II showed reductions to 60,24, 24 and 21%, maintained for at least 45 minutes. In both ipsilateral cortical regions reductions to 20/30, 12/9 and 14/19% were sustained for 45 minutes. An increase in latency times of not more than 45 msec was observed in these late waves.

With 5 mg/kg ketamine i.v. there was little change in the amplitude

of the *electrical* SEP, as shown in table 4.17. As with the higher doses, the amplitudes of peaks with latencies below 50 msec were not significantly changed. The peaks with latencies between 50-150 msec underwent reductions which were never greater than to 40% and in most cases not significant, except for the N R G C, thalamus and contralateral sensory cortex II and hypothalamus; a significant reduction, however, did not last more than 10 minutes. The peaks with latencies between 150-300 msec in the subcortical centers were reduced to 31-43% for a maximum of 45 minutes. The reductions in the contralateral sensory cortex I and II were to 20-27% for 20 minutes and in the ipsilateral cortex to 41-47% for 10-30 minutes. The very late waves were decreased more, to 21-40% for 20-45 minutes. The increase in latency was not greater than 25 msec, and there was sometimes even a decrease, except for the late wave in the amygdala.

A similar picture was seen in the mechanically evoked potential after administration of 5 mg/kg ketamine (Table 4.18).

There was a nonsignificant change in amplitude of those waves within 95 msec except for NRGC and thalamus where decreases, lasting for 10 minutes, to 47 and 64% occurred. The waves later than 95 msec were reduced in NRGC to 35-25%. Return to preanesthetic values was complete after 10-30 minutes. A similar reduction was seen in the thalamus, whereas in the hypothalamus there was no significant change. The 147 msec peak in the amygdala SEP was also not significantly changed, while the later one was reduced to 44% for 45 minutes. The contralateral cortex I also showed no significant change in the 127 msec component and a reduction to 42% in the very late wave, also for 45 minutes. In the contralateral cortex II the reductions were to 65 and 51% for 20 minutes, in the ipsilateral cortex I to 47 and 63% for 45 minutes and in the ipsilateral cortex II to 54 and 31% for 20-45 minutes. The very late wave of the hypothalamus was significantly reduced to 38%; 30 minutes later the reduction was no longer significant.

4.5.3. Discussion and conclusion

As with other anesthetics the components in the SEP with latencies smaller than 50 msec (the Aβ and Aγ fiber evoked potentials) were not significantly changed in ketamine anesthesia. The later components be-

tween 50 and 150 msec (Aδ evoked potential) and between 150 and 320 msec (C fiber evoked potential) are, however, interesting. The *electrically* evoked Aδ fiber response was reduced to 22-50% with the high dose of ketamine, to 17-64% with the medium dose and to 44-70% (mostly nonsignificant) with the low dose of ketamine.

The C fiber potential was even more reduced, to 10-41%, with the high dose of ketamine, to 18-32% with the medium dose and to 27-47% with the low dose.

The ipsilateral cortex I seemed to be less influenced, while the greatest reductions were seen in the ipsilateral cortex II. Of the subcortical structures the hypothalamus seemed to be the most resistant to ketamine.

In the *mechanically* evoked potential the Aδ potential was reduced to 17-38% with the high dose, to 9-60% with the medium dose and to 32-106% (mostly nonsignificant) with the low dose of ketamine. The C fiber potential was here also more strongly reduced, to 7-34% with the high dose, to 11-24% with the medium dose and to 25-63% with the low dose of ketamine.

The ipsilateral cortex I seemed to be less influenced too, but also the Aδ potential in the contralateral cortex II. The same region on the other side was the most influenced and the hypothalamus remained the most resistant to ketamine.

In monkeys the amplitudes of the *tooth-pulp* evoked potential were also reduced in the midbrain, in centrum medianum - nucleus parafascicularis complex - and almost 80% in the cortex after administration of 15 mg/kg ketamine (SPARKS et al.1975; PIMMEL et al. 1976).

A chemically related drug, phencyclidine, reduced the amplitudes of the visual, auditory and somatosensory evoked potential in rhesus monkeys. After 1-1.5 hour these amplitudes were the same as before administration of the drug (MATSUZAKI et al. 1980).

From these reports and our results it can be concluded that ketamine in a dose of 15 mg/kg gives sufficient anesthesia and analgesia for a period of 25-30 minutes, while 10 mg/kg is effective for 15-20 minutes. The effect of 5 mg/kg is doubtful; when stimuli of minor intensity, such as pricking the skin, are used, a sufficient effect seems to be produced for 5-10 minutes.

4.6. Effects of fentanyl on the SEP

4.6.1. Introduction

Analgesics are conventionally divided into two groups, narcotic analgesics and analgesic antipyretics. The oldest and best-known member of the first group is the alkaloid morphine, but this group contains not only drugs chemically related to morphine but a member of synthetic compounds of quite different structures. One of these is fentanyl, which reduces sensitivity to pain in all animals and causes respiratory depression. It is believed that fentanyl acts on the endorphin-binding sites near the periaqueductal gray, inhibiting the transmission of noxious messages to the central nervous system (BUCHSBAUM et al. 1981).

In dogs, rats and primates fentanyl induces sedation. It is often used with ataractics for neuroleptanalgesia in humans and animals. In this chapter the effects of two doses of fentanyl on the noxious *mechanically* and *electrically* evoked potentials will be discussed.

4.6.2. Results

The peak latency before the anesthetic, the maximum reduction, the significance ($p < 0.01$), the duration of this reduction, the time at which a significant reduction was no longer present, the maximum latency increment and the time at which the increment was observed are given.

Table 4.19 shows these data after administration of 0.075 mg/kg fentanyl i.v. The early waves, with latencies below 50 msec, were not significantly reduced except in the thalamus and hypothalamus.In these brain structures significant reductions, to 55 and 43%, were present for 20-30 minutes. A 0-10 msec increase in latency was seen within 30 minutes.

The later waves in the SEP of the NRGC were significantly reduced over a period of 100 minutes, the effect reaching a maximum of 37-25% at 5-10 minutes. The 67 msec peak and the very late wave (338 msec) in the thalamus SEP were decreased to 48-45%, this reduction lasting for 20-45 minutes; the intermediate wave showed a nonsignificant reduction (to 83%). The components in the hypothalamus SEP were successively reduced to 66% (not significant), to 59 and to 34%.

The very late components remained significantly reduced for two hours.

A 66% reduction was maintained in the amygdala for about one hour.

A similar decrease was seen in the contralateral cortex I, but there was no significant change in the last component of SEP of the contralateral cortex I, in the contralateral cortex II or the ipsilateral cortex I.

In the ipsilateral cortex II there was a reduction to 32-25%, lasting for one hour, in the waves between 50-150 msec, and a nonsignificant reduction in the very late wave.

After half an hour the latencies of the 50-150 msec components were increased by 15-75 msec and those with longer latencies by 20-100 msec.

The same dose of fentanyl also had a nonsignificant effect on the early (< 50 msec) components in the *mechanically* evoked potentials (Table 4.20.). In the later components of the SEP in the NRGC a strong reduction was maintained for two hours or more. In the thalamus the waves between 50-150 msec were significantly reduced to about 50% for 30 minutes, while the very late wave was not significantly reduced. In the hypothalamus the 56 msec wave was reduced to 36% for one hour, while the 116 msec component was not significantly changed. The very late wave, however, was reduced for a very long time, more than 2.5 hour, to 36%. The amygdala SEP was significantly reduced; the 93 msec component to 45% and the later ones to 22-26%. The SEP was decreased to 31-35% for 60-80 minutes in the contralateral cortex I. The components between 50-100 msec were equally reduced (to one third) in contralateral cortex II and ipsilateral cortex I.

The components over 100 msec in the contralateral somatosensory cortex II were not significantly changed, in the ipsilateral cortex I and II they were reduced to 35 and 32%.

A very large increase in latency times was seen after fentanyl, amounting to 20-100 msec in the 50-100 msec components and 30-150 msec in the later components. The maximum of this increase was reached in 20-60 minutes.

With 0.05 mg/kg fentanyl i.v. the *electrically* evoked potential was influenced as shown in table 4.21. Again the early components below 50 msec were not significantly changed except for the 43 msec wave in the thalamus and the 34 msec component in the hypothalamus, which were reduced to 41% for 45-80 minutes. Over a period

Table 4.19.EFFECTS OF FENTANYL (0.075 mg/kg) ON THE *ELECTRICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
SSC I contral.	18	100 N.S.	5		20	30
SSC I contral.	23	109 N.S.	5		31	30
N R G C	30	67 N.S.	10		25	20
Thalamus	40	55	5	30	52	5
Hypothalamus	42	43	10	20	51	20
SSC I contral.	31	56 N.S.	20		44	30
SSC II contral.	32	59 N.S.	30		36	30
SSC I ipsil.	31	90 N.S.	10		37	5
SSC II ipsil.	33	103 N.S.	5		56	30
N R G.C	64	37	10	100	76	30
Thalamus	67	48	5	20	105	45
Hypothalamus	68	66 N.S.	20		111	30
Amygdala	86	34	5	80	173	30
SSC I contral.	79	40	20	100	110	30
SSC II contral.	60	51 N.S.	20		94	45
SSC I ipsil.	76	53 N.S.	20		104	80
SSC II ipsil.	60	32	30	80	115	30
N R.G.C	138	25	5	100	170	30
Thalamus	134	83 N.S.	30		168	5
Hypothalamus	106	59	10	20	207	30
SSC II contral.	107	76 N.S.	45		109	60
SSC II ipsil.	40	25	20	60	169	5

Table 4.19. EFFECTS OF FENTANYL (0.075 mg/kg) ON THE *ELLECTRICALLY* EVOKED POTENTIALS *(continued)*

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
Thalamus	338	45	30	45	358	30
Hypothalamus	411	34	30	120	474	60
Amygdala	205	36	10	60	306	30
SSC I contral.	193	29	30	60	210	30
SSC II contral.	210	51 N.S.	10		252	20
SSC I ipsil.	273	41 N.S.	20		356	30
SSC II ipsil.	263	51 N.S.	30		304	20
Amygdala	406	26	45	80	440	30
SSC I contral.	320	66 N.S.	30		368	45

N.S. = Not Significant

Vertically the potentials with the same latency times (mean of six dogs) present in different brain centers are grouped together.
Horizontally the maximum reduction in amplitude (mean of six dogs), the time at which this reduction is present (mean of six dogs), the time at which the reduction is no longer significant, the maximum change in latency times (mean of six dogs) and the time at which this maximum is present (mean of six dogs), are shown.

Table 4.20.EFFECTS OF FENTANYL (0.075 mg/kg) ON THE *MECHANICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
SSC I contral.	24	108 N.S.	30		31	20
SSC II contral.	26	75 N.S.	20		39	60
N R G C	39	76 N.S.	30		46	20
SSC I contral.	31	73 N.S.	30		47	20
SSC II contral.	33	88 N.S.	30		44	30
SSC I ipsil.	40	63 N.S.	30		66	20
SSC II ipsil.	28	77 N.S.	30		40	45
N R G C	79	37	45	120	136	30
Thalamus	61	53	20	30	150	45
Hypothalamus	56	36	30	60	76	20
Amygdala	93	45	20	30	170	20
SSC I contral.	50	35	45	60	71	20
SSC II contral.	53	55	30	60	80	30
SSC I ipsil	95	53	20	30	162	30
SSC II ipsil.	65	35	30	80	101	30
Thalamus	136	47	20	30	268	45
Hypothalamus	116	64	20	30	265	45
Amygdala	122	22	20	80	211	20
SSC I contral.	93	31	60	80	121	60
SSC II contral.	128	60 N.S.	30		162	30
N R G C	248	6	60	> 150	316	30
Thalamus	254	61 N.S.	45		369	45
Hypothalamus	213	36	30	150	348	45
Amygdala	248	25	20	80	314	20
SSC I contral.	137	34	20	80	218	60
SSC II contral.	242	71 N.S.	30		301	60
SSC I ipsil.	231	35	45	100	296	30
SSC II ipsil.	219	32	45	60	248	45
Amygdala	372	26	20	60	406	30
SSC I contral.	330	63 N.S.	20		367	45

N.S. = Not Significant. For explanation: see Table 4.19.

of 80 minutes the later waves in the SEP of the N R G C sustained reductions to 43, 19 and 29%. The 50-100 msec components in the SEP of the other brain structures were not significantly changed, except in the contralateral sensory cortex I and the ipsilateral sensory cortex II, where reductions to 34 and 23% respectively were seen. After 80 minutes the values did not significantly differ from the preanesthetic recordings. The next waves, i.e. between 100-175 msec, were reduced in all structures to 25-48% except for the contralateral cortex II. The very late waves were significantly reduced in the subcortical structures, but no significant change was seen in the cortical structures.

The latencies between 50-100 msec were increased under fentanyl by 15-65 msec, the maximum effect being reached in 10-45 minutes. The components between 100 and 175 msec were increased by 10-80 msec and the last waves by 30-80 msec.

Table 4.22 shows the effects of this dose of fentanyl on the *mechanically* evoked potential. Here the early waves were also not significantly changed. The later waves in the SEP of the N R G C were reduced to 34 and 22% for 80 minutes. No significant change was seen in the thalamus. In the hypothalamus there were reductions to 43, 54 and 37%; the first and last ones remained below the preanesthetic level for 60-80 minutes, the middle one was not significantly reduced at all.

The SEP of the amygdala was reduced to 68% (not significant) and to 46 and 25% for 80-100 minutes. In the contralateral cortex I the 59 msec wave was not significantly changed; the two later waves showed reductions to 52 and 47%, maintained for 60-100 minutes. In the contralateral cortex II there was a decrease to 61-85%, which was not significant in the last two waves. In the ipsilateral cortex I the SEP was reduced nonsignificantly, except for a reduction to 30% in the last wave. The ipsilateral cortex II showed a reduction to 43-37% in the 50-175 msec component, while the last one was not significantly changed.

Again a quite large increase was seen in latencies: by 15-75 msec in the 50-100 msec component; by 20-82 msec in the 100-175 msec component and by 10-95 msec in the last component.

Table 4.21.EFFECTS OF FENTANYL (0.05 mg/kg) ON THE *FLECTRICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
SSC I contral.	17	102 N.S.	10		18	20
SSC I contral.	22	98 N.S.	10		34	20
SSC II contral.	24	81 N.S.	5		30	30
N R G C	33	64 N.S.	30		26	45
Thalamus	43	49	30	80	60	30
Hypothalamus	34	41	30	45	42	20
SSC I contral.	30	54 N.S.	20		45	20
SSC II contral.	47	57 N.S.	20		57	20
SSC I ipsil.	33	60 N.S.	45		42	20
SSC II ipsil.	37	70 N.S.	30		56	30
N R G C	67	43	30	80	96	45
Thalamus	90	80 N.S.	45		139	30
Hypothalamus	82	57 N.S.	30		124	20
Amygdala	68	75 N.S.	30		133	30
SSC I contral.	57	34	30	80	71	20
SSC II contral.	69	40 N.S.	20		92	10
SSC I ipsil.	62	47 N.S.	30		83	20
SSC II ipsil.	79	23	20	80	95	20
N R G C	139	19	20	80	204	30
Hypothalamus	167	43	30	60	287	20
Amygdala	125	32	20	80	213	45
SSC I contral.	109	30	60	120	121	30
SSC II contral.	112	79 N.S.	20		164	60
SSC II ipsil.	151	25	30	45	170	20

Table 4.21. EFFECTS OF FENTANYL (0.05 mg/kg) ON THE *ELECTRICALLY* EVOKED POTENTIALS *(continued)*

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
N R.G.C	272	29	20	80	342	45
Thalamus	232	48	20	30	285	45
Hypothalamus	362	45	5	30	401	20
Amygdala	294	25	45	60	337	45
SSC I contral.	223	62 N.S.	30		276	30
SSC II contral.	270	52 N.S.	20		299	10
SSC I ipsil.	213	44 N.S.	30		283	20
SSC II ipsil.	357	51 N.S.	30		285	30

N.S. = Not Significant

For explanation: see Table 4.19.

Table 4.22.EFFECTS OF FENTANYL (0.05 mg/kg) ON THE *MECHANICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
SSC I contral.	25	90 N.S.	45		29	20
SSC I contral.	31	81 N.S.	20		39	45
SSC I ipsil.	38	58 N.S.	30		43	30
SSC II ipsil.	35	65 N.S.	20		40	30
Thalamus	63	72 N.S.	30		76	20
Hypothalamus	81	43	30	60	150	30
Amygdala	68	68 N.S.	30		143	45
SSC I contral.	59	64 N.S.	30		89	20
SSC II contral.	63	61	30	45	69	20
SSC I ipsil.	86	58 N.S.	45		95	30
SSC II ipsil.	81	43	45	80	98	30
N.R G C	82	34	20	80	166	30
Thalamus	108	72 N.S.	20		118	45
Hypothalamus	107	54	20	80	187	30
Amygdala	169	46	20	100	204	45
SSC I contral.	120	52	30	100	141	20
SSC II contral.	131	85 N.S.	45		163	20
SSC II ipsil.	167	37	45	60	173	30
N R.G.C	209	22	45	80	315	20
Thalamus	277	65 N.S.	20		355	20
Hypothalamus	228	37	30	80	300	30
Amygdala	299	25	30	80	341	45
SSC I contral.	249	47	45	60	273	45
SSC II contral.	192	72 N.S.	45		234	20
SSC I ipsil.	177	30	45	100	332	30
SSC II ipsil.	319	62 N.S.	45		332	20

N.S. = Not Significant

For explanation: see Table 4.19.

4.6.3. Discussion and conclusion

Fentanyl has different effects on the different brain structures. Both low and high doses strongly decreased the SEP of the NRGC, with both *electrical* and *mechanical* stimulation. Reduction to 19-45% of the amplitude occurred in the 50-150 msec components (Aδ fiber evoked potential) while the reduction was even greater in the later, C fiber evoked components.

In the thalamus some differences were seen in the *electrically* and the *mechanically* evoked potentials. The early waves (< 50 msec) were reduced about 50% in the low and high dose experiments. This was also found by PLANCHE et al. (1979) in cats and by CHIN and DOMINO (1961) in dogs after morphine administration. The Aδ fiber evoked components were reduced to 48%, the second component nonsignificantly to 83%, with the high dose. With the low dose only one component in this range was observed; this was nonsignificantly changed (to 80%). The C fiber evoked potentials were reduced to 45-48% with both low and high doses of fentanyl.

In cats morphine reduces the 210 msec component in the *tooth-pulp* evoked potential in the centrum medianum (PLANCHE et al. 1979). In rats the reduction after morphine is as much as 60% in the posterior nuclear group of the thalamus with *tooth-pulp* stimulation (IRIKI and TODA 1980).

The response to *mechanical* stimulation in our experiments was less influenced in the thalamus, a nonsignificant reduction occurred in the C fiber evoked components (to 61-68%) and in the Aδ fiber components a nonsignificant reduction (to 72%) in the low dose experiments. Only in the high dose fentanyl group was a significant reduction (about 50%) seen in the Aδ fiber waves.

In the hypothalamus the first component of the *electrical* Aδ fiber evoked potentials were nonsignificantly changed (to 66 and 57%), the second one was reduced to 59 with the high and to 43% with the low dose. In the *mechanically* evoked potential the first Aδ fiber wave was more reduced than the second one. The C fiber waves were decreased to about 33% of their basic amplitudes in all experiments.

The reduction of the SEP with *mechanical* and *electrical* stimulation in the amygdala was comparable with that in the NRGC, being about 66% for the Aδ fiber potential and 75% for the C fiber potential, except

for the first wave of the Aδ fiber potential with the low dose of fentanyl, where no significant change was seen.

The high dose of fentanyl reduced the *electrical* and *mechanical* Aδ fiber and C fiber potentials in the contralateral cortex I to 33%. This reduction was also reached in the *electrical* Aδ fiber potential in the low dose experiment, while the *mechanical* Aδ fiber potential was reduced to 64 and 25%, the first peak nonsignificantly. The C fiber potential with the low dose was reduced nonsignificantly in *electrical* stimulation and to 47% in *mechanical* stimulation. The very late component present in the high dose experiments was not significantly reduced in either the *electrical* or the *mechanical* series.

In the contralateral cortex II hardly any significant change was seen, with either high or low doses of fentanyl. Only the first *mechanically* evoked Aδ fiber potential was reduced to 55% with the high dose and to 61% with the low dose. The mean of values in all dogs remained rather high but never exceeded 50%.

IRIKI and TODA (1980) obtained comparable results in rats. Morphine reduced the amplitudes in the *tooth-pulp* evoked potentials more in the sensory cortex I (70%) than in the sensory cortex II (40%).

In the ipsilateral cortex these effects seem to be switched. The *electrically* evoked potential was barely significantly changed in the ipsilateral cortex I while the Aδ fiber evoked components were reduced to almost 25% in the ipsilateral cortex II. The mechanical response was similar, a reduction to 53% and a nonsignificant reduction to 58% in the Aδ fiber potential in ipsilateral S I and to 35%, 43%, 37% in the ipsilateral S II.

In the C fiber range a nonsignificant change was seen, to about 40-50%, in the *electrically* evoked potential ipsilaterally in both S I and S II. The *mechanically* evoked potential was reduced to 30-45% in S I and 32% in S II with the low dose. The very early potentials, i.e. those before the Aδ and C fiber potentials, were not significantly changed in any cortical structure, as was also found by CHIN and DOMINO (1961) after administration of morphine in dogs. In guineapigs morphine had no effect at all on the SEP of the cortex (MOYANA et al. 1975), but unfortunately the blank response had been obtained under pentobarbital anesthesia while the authors concluded that pentobarbital had no effect on

the SEP in guineapigs. In our experiments in dogs an effect of pentobarbital on the SEP was in fact demonstrated (see the foregoing).

The above-named authors found an increase in latency after administration of pentazocine. An increase in latency in all brain structures was also found in our experiments. The least increases were observed in the contralateral cortex I, the contralateral cortex II, the ipsilateral cortex II and the ipsilateral cortex I, in that order; comparable increases in latencies were seen in the N R G C Larger increases in latencies were noted in the thalamus, hypothalamus and the amygdala, in that order. In human subjects the administration of morphine or its derivatives gave similar results; morphine reduced the 120 msec component in the *tooth-pulp* evoked potential significantly (NABER et al.1980; BUCHSBAUM et al. 1981), and pethidine gave the same effects (SCHMIDT 1970). The reduction was neutralized by naloxone, a morphine antagonist (NABER et al. 1980). Persons with low β-endorphin (naturally occurring morphine-like substance) levels experience more pain relief after morphine than persons with high β-endorphin levels (NABER et al. 1980). Naloxone produced, in pain-insensitive persons, (high endorphin level) a hyperanalgesic state, with an increase in the 76-112 msec, 116-152 msec and 168-248 msec components of the *electrically* evoked somatosensory potential. Individuals who are very sensitive to pain (low endorphin levels) develop hypalgesia after naloxone administration. Endomorphins thus have a modulatory effect on pain in both ways (BUCHSBAUM et al. 1977). It is possible that endorphin level differences between the dogs may be involved in our experiments. Classification of pain-sensitive and pain-insensitive dogs in behavioral tests is difficult. Morphine, and also fentanyl, can reduce the amplitudes and increase the latencies of *mechanically* and *electrically* evoked potentials.

Especially the SEP in the NRGC and in the amygdala are easily reduced. Less sensitive to fentanyl are the hypothalamus, the thalamus, the contralateral cortex I and the ipsilateral cortex II. Fairly resistant to fentanyl seem to be the ipsilateral cortex I and the contralateral cortex II. Aδ fiber potentials seem to be a little more influenced by the same dose of fentanyl than the C fiber potentials; 0.05 mg/kg seemed to give insufficient pain relief in all dogs; 0.075 mg/kg may be enough to give relief of pain when light nociceptive sti-

mulation is used; a higher dose seems to be needed to ensure that in all dogs a sufficient pain relief is achieved.

4.7. Effects of droperidol and xylazine on the SEP

4.7.1. Introduction

Droperidol is thought to have an inhibitory effect on the arousal response in the reticular activating system, this inhibition being probably mediated through the basal ganglia of the caudate loop (VENNING 1963). JANSSEN (HAASE and JANSSEN 1965) has shown that droperidol has an inhibitory effect on behavior in rats and dogs which resembles closely that described by BUCHWALD when he stimulated the caudate nucleus of cats with carbachol (BUCHWALD and LING 1965).

Droperidol, a neuroleptic agent which can be given by intramuscular injection, is the most potent antiemetic known. It is said to antagonize the respiratory depressant effect of morphine-like compounds by increasing the sensitivity of the respiratory center to carbon dioxide. In association with fentanyl it is used for neuroleptalgesia in dogs.

Xylazine, which was first synthesized in 1962, can be used to produce depression of the central nervous system, ranging from mild sedation to deep basal narcosis. Some reports indicate that xylazine produces analgesia in cattle, and surgical operations have been performed under the sedation produced by this compound on its own. Others have reported an absence of demonstrable analgesia, and have found that, for surgery, supplementation with a general anesthetic or the use of local analgesia was essential to prevent movement in response to painful stimulation(HALL 1967).

In the following paragraph the effects of droperidol in doses of 1.5 and 1.0 mg/kg i.v. and of xylazine in the same doses on the noxious *electrical* and *mechanical* somatosensory potentials are reported.

4.7.2. Results

A dose of 1.5 mg/kg droperidol influenced the noxious *electrically* evoked potentials as shown in table 4.23.

Most of the components in the different brain structures were not significantly reduced, only the 51 msec in the contralateral somatosensory cortex I was reduced to 65%, this reduction lasting for 45 mi-

nutes.

The very late wave in the SEP of the hypothalamus (378 msec) was also significantly reduced, to 45%, for 1 hour.

A very slight increase in latency, not exceeding 25 msec was noted; in the very late waves this was replaced by a decrease. Table 4.24 shows the effect of the same dose on the *mechanical* somatosensory evoked potential; here a nonsignificant decrease in amplitudes occurred, except for the 61 msec wave in the SEP of the hypothalamus, the 93 msec in the NRGC, the 113 msec wave in the ipsilateral somatosensory cortex 1, the 173 msec in the hypothalamus and the very late waves in the thalamus and hypothalamus. The reduction of these waves in these few brain structures lasted in some cases for 80 minutes. An increase of latencies was also seen in these *mechanically* evoked potentials, 35 msec for the waves below 150 msec and 80 msec for the later components. The very late wave showed mainly a decrease in latency. A lower dose of droperidol (1.0 mg/kg) did not significanly change the amplitudes of *electrically* evoked SEP (Table 4.25.). The mean of the reduced values in all dogs never fell below 52%. An increase in latencies by a maximum of 25 msec was reached within 60 minutes. A similar picture was obtained for the *mechanically* evoked potentials after 1.0 mg/kg droperidol intravenously (Table 4.26.).

Except for the 274 msec in the SEP of the ipsilateral cortex 1, no wave was significantly reduced; the mean reduction was never to a value below 54%. A slight (smaller than 25 msec) increase in latency was also found.

The effects of 1.5 mg/kg xylazine on the *electrically* evoked potentials are shown In table 4.27. The early potentials were not significantly changed in amplitude; their latency times increased slightly, this increment being most pronounced in the thalamus. The later waves, over 50 msec peak latency were reduced to 48 and 38% in the NRGC; in the thalamus they were reduced nonsignificantly and to 43%. The three later waves in the SEP of the hypothalamus were not significantly changed. Of the two later waves in the amygdala, the first one was not significantly changed, the second was reduced to 41%.

In the contralateral somatosensory cortex 1, three later waves were present; the middle one was not significantly changed in amplitude;

Table 4.23. EFFECTS OF DROPERIDOL (1.5 mg/kg) ON THE *ELECTRICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE		TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
SSC I contral.	20	99	N.S.	30			
SSC I contral.	25	91	N.S.	10			
SSC II contral.	24	88	N.S.	30		28	60
SSC I ipsil.	23	68	N.S.	20		25	80
Thalamus	41	71	N.S.	30		44	20
Hypothalamus	40	76	N.S.	5		52	45
Amygdala	39	64	N.S.	5		47	45
SSC I contral.	33	77	N.S.	5		37	60
SSC II contral.	34	82	N.S.	5		36	45
SSC I ipsil.	39	70	N.S.	20		37	45
SSC II ipsil.	28	92	N.S.	5		29	60
N R G C	59	82	N.S.	5		66	80
Thalamus	67	98	N.S.	5		74	20
Hypothalamus	72	81	N.S.	5		88	80
Amygdala	85	77	N.S.	5		91	45
SSC I contral.	51	65		30	45	53	60
SSC II contral.	63	99	N.S.	45		70	60
SSC I ipsil.	71	83	N.S.	20		86	30
SSC II ipsil.	65	91	N.S.	5		70	45
N R G C	121	84	N.S.	5		133	80
Thalamus	99	90	N.S.	10		106	10
SSC I contral.	89	85	N.S.	30		96	45
SSC II contral.	114	88	N.S.	5		131	45
SSC I ipsil.	121	94	N.S.	5		165	60

Table 4.23. EFFECTS OF DROPERIDOL (1.5 mg/kg) ON THE *ELECTRICALLY* EVOKED POTENTIALS *(continued)*

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
Thalamus	174	74 N.S.	10		205	20
Hypothalamus	167	84 N.S.	10		175	60
Amygdala	172	89 N.S.	5		196	20
SSC I contral.	155	81 N.S.	5		414	60
SSC II contral.	238	81 N.S.	20		169	60
SSC I ipsil.	257	70 N.S.	10		262	20
SSC II ipsil.	302	67 N.S.	5		282	60
Thalamus	336	71 N.S.	60		320	60
Hypothalamus	378	45	10	60	205	5
Amygdala	371	62 N.S.	20		313	30
SSC I contral.	348	82 N.S.	5		255	45
SSC II contral.	329	61 N.S.	60		341	45

N.S. = Not Significant

Vertically the potentials with the same latency times (mean of six dogs) present in different brain regions are grouped together.
Horizontally the maximum reduction in amplitude (mean of six dogs), the time at which this reduction is present (mean of six dogs), the time at which this reduction is no longer significant, the maximum change in latency times (mean of six dogs) and the time at which this reduction is present (mean of six dogs), are shown.

Table 4.24.EFFECTS OF DROPERIDOL (1.5 mg/kg) ON THE *MECHANICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
SSC I contral.	26	103 N.S.	30		29	45
SSC II contral.	23	101 N.S.	30		29	60
SSC I contral.	34	75 N.S.	20		37	80
SSC II contral.	30	68 N.S.	20		36	60
SSC I ipsil	42	75 N.S.	30		58	80
SSC II ipsil.	34	81 N.S.	20		43	30
Thalamus	52	78 N.S.	20		56	60
Hypothalamus	61	51	20	30	66	30
SSC I contral.	55	86 N.S.	30		63	45
SSC II contral.	52	76 N.S.	45		54	45
SSC I ipsil.	69	59 N.S.	20		82	60
SSC II ipsil.	71	97 N.S.	30		79	60
N R G C	93	70	20	30	114	30
Thalamus	114	77 N.S.	20		138	60
Hypothalamus	83	68 N.S.	20		105	30
Amygdala	110	75 N.S.	30		122	80
SSC I contral.	106	80 N.S.	20		124	45
SSC II contral.	130	97 N.S.	20		155	60
SSC I ipsil.	113	42	30	80	147	30
SSC II ipsil.	142	91 N.S.	30		157	30
N R G C	229	74 N.S.	30		280	30
Thalamus	167	75 N.S.	30		195	60
Hypothalamus	173	43	45	80	190	80
Amygdala	213	86 N.S.	20		292	80
SSC I contral.	265	87 N.S.	30		250	60
SSC II contral.	291	74 N.S.	45		280	60
SSC I ipsil.	220	43 N.S.	30		257	30
SSC II ipsil.	354	62 N.S.	45		367	20
Thalamus	402	46	30	45	328	30
Hypothalamus	289	55	30	60	311	60
Amygdala	408	67 N.S.	30		355	20

N.S. = Not Significant. For explanation: see Table 4.23.

the first and the last were reduced to 60 and 56% respectively. In the contralateral cortex II significant reductions were seen, to 59, 51 and 37% of the preanaesthetic amplitudes.

The amplitudes of the first of the later waves in the SEP of both the ipsilateral somatosensory cortex structures were not significantly changed; the next wave was reduced to 61% in ipsilateral SSC I and non-significantly in ipsilateral SSC II; the last wave in each of these two cortical regions was reduced to 40%. If the reduction was significant it reached its maximum within 30 minutes. The peaks with latencies between 50 and 100 msec had their latencies increased by a maximum of 25 msec under xylazine. The later waves sometimes underwent an increase of 200 msec. All these increases in latency were present within 60 minutes.

The same dose of xylazine influenced the *mechanical* SEP as shown in table 4.28. The early waves with latencies smaller than 80 msec were not significantly changed. In the N R G C the later waves were reduced to 49 and 32% respectively for 80-100 minutes. In the thalamus the later waves were reduced to 47 and 43% for 45-60 minutes. The very late wave was not significantly changed. Of the three later waves in the hypothalamus SEP, the first one was not significantly changed; the next two were decreased to 27 and 38% for 45 minutes. In the amygdala SEP two later waves were reduced to 42 and 27% also for 45 minutes. The later components in the contralateral cortex I were not significantly changed.

In the contralateral SSC II the SEP was non significantly reduced in the later components under 150 msec, but was reduced to 59% for 30 minutes in the 284 msec peak. The SEP in the ipsilateral cortex I was reduced to 60%. In the ipsilateral cortex II there was no significant change at all in amplitude. In all brain centers there was a large increase in latency times, even to 40 msec for the early peaks and to 60 msec for the later components.

A smaller dose of xylazine (1.0 mg/kg) caused little reduction in the amplitudes in the electrical SEP (Table 4.29.). Only the 74 msec wave in the NRGC SEP, the 331 msec in the thalamus-SEP, the 258 msec peak in the amygdala SEP, the 296 msec wave in the contralateral cortex I SEP, the 265 msec peak in the contralateral SSC II SEP and the 298 msec component in the ipsilateral cortex I SEP were significantly reduced; this reduction was never to a lower value than 37% and lasted for at most 45 minutes.

Table 4.25 EFFECTS OF DROPERIDOL (1.0 mg/kg) ON THE *ELECTRICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
SSC I contral.	18	99 N.S.	5			
SSC I contral.	24	105 N.S.	10			
N R G C	32	94 N.S.	30			
Thalamus	42	68 N.S.	30			
Hypothalamus	38	80 N.S.	20		44	45
SSC I contral.	32	84 N.S.	30		35	30
SSC II contral.	37	87 N.S.	5			
SSC I ipsil.	33	88 N.S.	30		37	30
SSC II ipsil.	36	89 N.S.	20			
N R G C	66	81 N.S.	20		71	45
Thalamus	68	93 N.S.	30		72	20
Hypothalamus	77	86 N.S.	10		84	60
Amygdala	75	78 N.S.	10		98	60
SSC I contral.	47	65 N.S.	30		50	30
SSC II contral.	57	83 N.S.	20		66	60
SSC I ipsil	57	93 N.S.	30		64	30
SSC II ipsil.	65	87 N.S.	30		67	60
Thalamus	100	84 N.S.	30		110	45
Hypothalamus	113	92 N.S.	30		120	20
Amygdala	128	84 N.S.	60		163	60
SSC I contral.	93	83 N.S.	45		100	30
SSC II contral.	124	86 N.S.	30		134	60
SSC I ipsil.	80	75 N.S.	20		88	45
SSC II ipsil.	128	90 N.S.	30		122	60
Hypothalamus	138	102 N.S.	5		146	20
SSC I contral.	128	82 N.S.	20		156	45
SSC I ipsil.	136	78 N.S.	20		146	45

Table 4.25. EFFECTS OF DROPERIDOL (1.0 mg/kg) ON THE *ELECTRICALLY* EVOKED POTENTIALS *(continued)*

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
N R G C	169	87 N.S.	20		191	30
Thalamus	258	82 N.S.	45		292	30
Hypothalamus	268	98 N.S.	30		300	45
Amygdala	230	95 N.S.	5		259	20
SSC I contral.	198	90 N.S.	20		225	20
SSC II contral.	269	75 N.S.	30		284	45
SSC I ipsil.	297	63 N.S.	5		271	5
SSC II ipsil.	258	90 N.S.	30		283	30
Hypothalamus	367	52 N.S.	30		425	45
SSC I contral.	271	56 N.S.	10		286	20

N.S. = Not Significant

For explanation: see Table 4.23.

Table 4.26. EFFECTS OF DROPERIDOL (1.0 mg/kg) ON THE *MECHANICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
SSC I contral.	21	104 N.S.	20		23	45
SSC I contral.	29	92 N.S.	30		29	60
SSC II contral.	25	97 N.S.	30		25	30
Thalamus	44	86 N.S.	20		62	60
Hypothalamus	37	54 N.S.	20		46	60
SSC I contral.	37	87 N.S.	20		39	60
SSC II contral.	41	100 N.S.	45		50	30
SSC I ipsil.	40	79 N.S.	20		44	60
SSC II ipsil.	32	83 N.S.	45		36	45
N R G C	85	93 N.S.	30		106	45
Thalamus	62	83 N.S.	30		69	20
Hypothalamus	63	74 N.S.	45		73	20
Amygdala	53	99 N.S.	20		65	60
SSC I contral.	56	81 N.S.	45		59	30
SSC II contral.	56	79 N.S.	20		70	45
SSC I ipsil.	69	79 N.S.	30		82	30
SSC II ipsil.	70	98 N.S.	30		76	45
Thalamus	105	92 N.S.	30		127	45
Hypothalamus	96	98 N.S.	45		110	20
Amygdala	89	88 N.S.	20		103	60
SSC I contral.	109	83 N.S.	45		119	30
SSC II contral.	133	101 N.S.	30		154	45
SSC I ipsil.	94	63 N.S.	20		131	45
SSC II ipsil.	157	96 N.S.	45		168	20

Table 4.26. EFFECTS OF DROPERIDOL (1.0 mg/kg) ON THE *MECHANICALLY* EVOKED POTENTIALS *(continued)*

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
N R G C	249	80 N.S.	20		289	45
Thalamus	310	83 N.S.	20		368	45
Hypothalamus	153	82 N.S.	20		188	20
Amygdala	169	85 N.S.	3'		181	30
SSC I contral	222	80 N.S.	20		239	30
SSC II contral.	246	90	45		279	60
SSC I ipsil.	274	68 N.S.	30	60	312	60
SSC II ipsil.	276	87 N.S.	30		256	30
Hypothalamus	346	97 N.S.	30		372	30
Amygdala	402	72 N.S.	20		376	20

N.S. = Not Significant

For explanation: see Table 4.23.

Table 4.27. EFFECTS OF XYLAZINE (1.5 mg/kg) ON THE *ELECTRICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
SSC I contral.	18	107 N.S.	10			
SSC I contral.	24	103 N.S.	10			
SSC II contral.	28	98 N.S.	20			
N R G C	36	97 N.S.	5			
Thalamus	45	79 N.S.	30		83	20
Hypothalamus	39	80 N.S.	20		43	20
Amygdala	45	78 N.S.	10		47	20
SSC I contral.	31	80 N.S.	5		43	80
SSC II contral.	38	81 N.S.	5		45	60
SSC I ipsil.	36	107 N.S.	20		42	80
SSC II ipsil.	38	94 N.S.	20			
N R G C	66	48	10	20	80	45
Hypothalamus	63	81 N.S.	5		78	20
Amygdala	86	73 N.S.	20		111	20
SSC I contral.	49	60	20	60	58	60
SSC II contral.	56	59	30	45	68	20
SSC I ipsil.	50	81 N.S.	20		64	10
SSC II ipsil.	65	71 N.S.	20		85	20
Thalamus	102	61 N.S.	5		157	5
SSC I contral.	100	63 N.S.	20		112	60
SSC II contral.	88	51	20	30	141	10
SSC I ipsil.	105	61	20	30	116	30
SSC II ipsil.	130	78 N.S.	20		173	20

Table 4.27. EFFECTS OF XYLAZINE (1.5 mg/kg) ON THE *ELECTRICALLY* EVOKED POTENTIALS *(continued)*

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
N R G C	198	38	5	30	299	5
Thalamus	287	43	10	20	365	10
Hypothalamus	156	65 N.S.	10		223	10
Amygdala	217	41	5	10	251	5
SSC I contral.	259	56	10	20	295	30
SSC II contral.	174	37	5	45	204	10
SSC I ipsil.	292	41	5	30	328	10
SSC II ipsil.	284	40	30	45	302	20

N.S. = Not Significant

For explanation: see Table 4.23.

Table 4.28.EFFECTS OF XYLAZINE (1.5 mg/kg) ON THE *MECHANICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
SSC I contral.	26	93 N.S.	30		28	30
SSC II contral.	30	82 N.S.	45		36	30
Hypothalamus	45	78 N.S.	45		63	20
SSC I contral.	35	71 N.S.	20		37	20
SSC II contral.	43	88 N.S.	20		49	30
SSC I ipsil.	47	85 N.S.	20		55	30
SSC II ipsil.	36	71 N.S.	30		50	30
Thalamus	64	66 N.S.	20		69	45
Hypothalamus	76	58 N.S.	30		117	30
Amygdala	79	77 N.S.	30		105	20
SSC I contral.	54	75 N.S.	30		59	20
SSC II contral.	66	83 N.S.	30		84	45
SSC I ipsil.	69	82 N.S.	20		92	45
SSC II ipsil.	67	63 N.S.	30		91	30
N R G C	85	49	45	80	117	60
Thalamus	101	47	30	60	152	60
Hypothalamus	111	60 N.S.	30		171	30
Amygdala	133	42	20	45	186	30
SSC I contral.	107	72 N.S.	20		110	45
SSC II contral.	128	74 N.S.	20		169	30
SSC I ipsil.	156	61	30	60	161	30
SSC II ipsil.	156	54 N.S.	45		211	30
SSC I contral.	134	68 N.S.	20		146	80

Table 4.28.EFFECTS OF XYLAZINE (1.5 mg/kg) ON THE *MECHANICALLY* EVOKED POTENTIALS *(continued)*

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
N R G C	207	32	45	100	267	30
Thalamus	159	43	30	45	191	20
Hypothalamus	193	27	30	45	260	30
Amygdala	305	27	20	45	331	30
SSC I contral.	276	71 N.S.	30		287	45
SSC II contral.	284	54	20	30	298	45
SSC I ipsil.	245	59	20	30	261	30
SSC II ipsil.	304	53 N.S.	30		317	45
Thalamus	344	51 N.S.	20		394	45
Hypothalamus	393	38	30	45	405	45

N.S. = Not Significant

For explanation: see Table 4.23.

Table 4.29. EFFECTS OF XYLAZINE (1.0 mg/kg) ON THE *ELECTRICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
SSC I contral.	18	106 N.S.				
SSC I contral.	24	99 N.S.	5		26	30
SSC II contral.	26	111 N.S.				
Thalamus	41	78 N.S.	10		58	10
Hypothalamus	32	79 N.S.	5		36	10
SSC I contral.	30	79 N.S.	20		33	5
SSC II contral.	33	84 N.S.	5			
SSC I ipsil.	34	74 N.S.	20		40	30
SSC II ipsil.	40	96 N.S.	10		46	10
N R G C	74	59	5	20	106	5
Thalamus	66	88 N.S,	10		101	10
Hypothalamus	50	71 N.S.	5		49	5
Amygdala	61	76 N.S.	20		87	20
SSC I contral.	49	54 N.S.	10		53	30
SSC II contral.	58	94 N.S.	5		50	20
SSC I ipsil.	57	80 N.S.	5		70	10
SSC II ipsil.	65	78 N.S.	10		87	10
Thalamus	110	80 N.S.	10		188	10
Hypothalamus	85	72 N.S.	5		96	10
Amygdala	117	63 N.S.	20		154	30
SSC I contral.	97	75 N.S.	10		118	30
SSC II contral.	119	65 N.S.	20		154	5
SSC I ipsil	92	59 N.S.	10		110	10
SSC II ipsil.	152	76 N.S.	20		163	20

Table 4.29. EFFECTS OF XYLAZINE (1.0 mg/kg) ON THE *ELECTRICALLY* EVOKED POTENTIALS *(continued)*

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
N R G C	192	76 N.S.	5		204	20
Hypothalamus	159	75 N.S.	10		183	5
SSC I contral.	160	56 N.S.	5		176	10
N R G C	307	69 N.S.	20		331	5
Thalamus	331	45	5	10	400	30
Hypothalamus	323	75 N.S.	30		341	30
Amygdala	258	49	5	20	263	5
SSC I contral.	296	61	5	20	318	30
SSC II contral.	265	37	5	45	250	5
SSC I ipsil.	298	38	10	20	332	20
SSC II ipsil.	350	49 N.S.	5		365	20

N.S. = Not Significant

For explanation: see Table 4.23.

Table 4.30.EFFECTS OF XYLAZINE (1.0 mg/kg) ON THE *MECHANICALLY* EVOKED POTENTIALS

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
SSC I contral.	21	100 N.S.				
SSC I contral.	28	99 N.S.	20		33	30
Thalamus	46	65 N.S.	20		40	20
Hypothalamus	47	72 N.S.	30		79	45
SSC I contral.	35	71 N.S.	20		36	30
SSC II contral.	32	87 N.S.	45		33	45
SSC I ipsil.	38	85 N.S.	45		46	20
SSC II ipsil.	35	107 N.S.	30		36	30
N R G C	86	56	20	45	106	20
Thalamus	71	84 N.S.	20		76	20
Hypothalamus	89	66 N.S.	30		118	20
Amygdala	81	79 N.S.	20		90	20
SSC I contral.	52	85 N.S.	30		69	30
SSC II contral.	51	93 N.S.	30		54	30
SSC I ipsil.	63	78 N.S.	45		83	20
SSC II ipsil.	73	85 N.S.	20		76	30
Thalamus	106	89 N.S.	20		151	30
SSC II contral.	85	84 N.S.	20		103	45
SSC I ipsil.	114	70	20	30	164	30
N R G C	192	56	20	45	203	20
Thalamus	186	79 N.S.	20		219	20
Hypothalamus	196	50	20	30	213	30
Amygdala	187	54	20	45	191	20
SSC I contral.	129	82 N.S.	20		130	30
SSC II contral.	147	47	30	45	152	30
SSC I ipsil.	176	49	20	30	229	30
SSC II ipsil.	133	84 N.S.	20		156	30

Table 4.30. EFFECTS OF XYLAZINE (1.0 mg/kg) ON THE *MECHANICALLY* EVOKED POTENTIALS *(continued)*

BRAIN REGION	PEAK LAT T BEFORE	MAXIMUM REDUCTION TILL...PERCENTAGE	TIME OF MAXIMUM REDUCTION IN MIN	RETURN PRE-ANESTHETIC VALUES	MAXIMUM CHANGE LAT T	TIME OF MAXIMUM CHANGE IN MIN
Thalamus	340	70 N.S.	20			
Hypothalamus	318	63 N.S.	20		348	20
Amygdala	318	54 N.S.	30		359	60
SSC I contral.	348	80 N.S.	20		273	30
SSC II contral.	261	43	20	60	245	30
SSC II ipsil.	277	80 N.S.	30		282	30

N.S. = Not Significant

For explanation: see Table 4.23.

There was also a very large increase in latency, with a maximum of 35 msec, for the early components, and 75 msec for the later components.

The *mechanical* SEP was slightly more influenced by the same dose of xylazine (Table 4.30.); the NRGC SEP was reduced to 56% for 45 minutes; the 196 msec component of the hypothalamus SEP was reduced to 50% for half an hour and the same wave in the amygdala SEP was reduced to 54% for 45 minutes. In the cortex, the components with latencies above 100 msec were significantly reduced in the contralateral somatosensory cortex II and the ipsilateral somatosensory cortex I to about 40-70% for 30-60 minutes. An increase in latency times was also seen, about 0-20 msec in the components under 100 msec and 1-55 msec for the components under 200 msec. The later components sometimes increased and sometimes decreased in latency after xylazine administration.

4.7.3. Discussion and conclusion

Although both droperidol and xylazine are described as sedatives their effects on the nociceptive evoked potentials are by no means alike.

Droperidol in a dose of 1.0 mg/kg intravenously did not significantly change the amplitudes of either the *electrically* or the *mechanically* evoked potentials. A tendency to reduction was present but the mean reduction in 5 dogs never exceeded 30%. A 50% increase in dose did influence the amplitudes a little more, but hardly any significant reduction was seen in most brain structures; in some structures 43% of the preanesthetic level was reached.

There was also a tendency to increasing latencies, but the change remained very small. Another sedative, chlorpromazine, has also been shown not to cause any significant change in somatosensory cortical evoked potentials in human subjects, although a tendency to amplitude decrease and latency increase was noted (BAUST et al. 1977; SALETU et al. 1972).

Xylazine (1.0 mg/kg) also did not significantly change the *electrical* and *mechanical* Aδ fiber components in the SEP, except for the NRGC where a significant reduction was seen. The later components, > 150 msec i.e. C fiber response, were significantly changed in the contralateral

somatosensory cortex II and the ipsilateral somatosensory cortex I and also in the *electrical* SEP of the thalamus, the amygdala and the contralateral somatosensory cortex I. These C fiber waves were also significantly changed in the N R G C and the amygdala after *mechanical* stimulation. A 50% higher dose of xylazine reduced the Aδ fiber potential in the N R G C and in the *mechanical* SEP in the thalamus, in addition to one component in the amygdala and in the *electrical* SEP of the contralateral cortex I. This dose of xylazine also reduced the C fiber potential significantly, except for the *electrical* hypothalamic SEP and the *mechanical* SEP in the contralateral somatosensory cortex II. A latency shift was seen in the SEP of all brain structures under xylazine, this effect being more pronounced in the later waves than in the early ones.

In conclusion it can be said that droperidol has only minor effects on the SEP and has therefore no analgesic action. Xylazine, on the other hand, tends to reduce the nociceptive evoked potentials at a dose higher than 1.5 mg/kg. This dose seems to be too low for some dogs. Xylazine has more effects on the C fiber components in the SEP than on the Aδ fiber components. The *electrical* SEP seems also to be more influenced by xylazine, while the hypothalamus, the contralateral cortex I and the ipsilateral cortex II are more resistant to this drug. The N R G C seems to be most sensitive of all brain structures investigated in this study.

CHAPTER 5

GENERAL DISCUSSION AND CONSLUSION

Evoked potentials have a number of peaks, each with a different latency time. Different methods of stimulation, however, such as *electrical tooth-pulp stimulation, mechanical stimulation of the skin* with a needle and *electrical stimulation of the skin* all seem to produce the same configuration of evoked potentials in different brain nuclei. It would appear that the peaks with different latency times are the consequence of differences in conduction velocity among the peripheral nerves and of the existence of nerve-cell networks. These nerves are composed of fibers which are classified as Aα, Aβ, Aγ, Aδ and C fibers; their conduction velocities and the thickness of their myelin sheaths decrease in this order. The C fibers have practically no myelin sheath.

The Aδ and C fibers are those which react to nociceptive stimulation of the skin and thus are the fibers involved in pain perception.

In Chapter 3 the latency times and amplitudes of the various peaks in the evoked potentials are reported in the order peripheral nerve, spinal cord, brain. This is also the order in which the potentials appear.From these data it is also evident that the various peaks in the evoked response originate from nerve fibers with different conduction velocities.The Aα, Aβ and Aγ fibers give rise to potentials in the brain with latency times of less than 50 msec.

In the brain the evoked potentials produced by Aδ fibers fall between 50 and 150 msec and those produced by the C fibers between 150 and 200 msec. When the intensity of stimulation of the skin is increased, so that especially the 'pain fibers' are stimulated, the amplitudes of those potentials also increase. These are just the potentials which are influenced by anesthetics; the early potentials with latencies of less than 50 msec remain practically unchanged, without any significant decrease in amplitude, whereas the potentials with latencies of more than 50 msec are strongly influenced by anesthetics, as described in Chapter 4.

Local anesthetics produce a large decrease in amplitude and a small increase in latency time. Halothane and nitrous oxide, two inhalation anesthetics, also produce a large reduction of amplitude and a fairly large increase of latency, although this requires a high concentration of

halothane. Pentobarbital, a narcotic,likewise produces a large and long-lasting reduction of amplitude and a large increase of latency time. Thiopental, another narcotic, has a similar effect but of shorter duration. Ketamine, a general anesthetic, is a good analgesic, as shown by the reduction in amplitude of the potentials evoked by Aδ and C fibers. Fentanyl, a morphine derivative, had only a slight effect in the dosage used by us, and the same was true of xylazine, a sedative, while droperidol, a sedative, caused hardly any reduction in amplitude and only a slight increase in latency time.

From the foregoing it may be concluded that measurement of evoked potentials is a fairly reliable method for ascertaining the degree to which nociceptive stimuli are reaching the brain; if no or practically no potentials are evoked by the nerve fibers which conduct nociceptive stimuli, we are justified in concluding that good analgesia has been attained.

Comparison of the various brain regions leads to the following conclusions: The nucleus reticularis gigantocellularis is affected fairly rapidly by anesthetics; the hypothalamus and amygdala react to about the same degree but are somewhat more resistant than the N R G C; the thalamus is more rapidly affected than the sensory cortex, of which part II remains active for quite a long time under the action of anaesthetics.

Measurement of potentials in the two cortical regions only, both left and right, should be sufficient for evaluation of the analgesic potency of pain-killers and anesthetics.

SOMATOSENSORY EVOKED POTENTIALS IN RELATION TO ANESTHESIA

This study was designed to seek an answer to the following questions: does registration of somatosensory evoked potentials (SEP) give an indication of the degree to which noxious (painful) stimuli reach the central regions of the brain and does it thus provide a 'scale' of the degree to which these stimuli are felt as 'pain', so that the efficacy of anesthesia or analgesia can be 'measured' from the decrease in intensity of these potentials?

Chapter 1 deals with the neurophysiology of pain. Peripheral nerves are made up of fibers of different thickness, depending on the thickness of the myelin sheath. From thicker to thinner they are classified as Aα, Aβ, Aγ, Aδ and C fibers, the A fibers being myelinated and the C fibers not. The thicker the myelin sheath the greater is the velocity of conduction in the nerve fiber. Slowly conducting, Aδ and C fibers have been shown to be involved in transmission of signals from tissue-damaging and hence painful stimuli. In the spinal cord these fibers relay to ascending nerve tracts which convey the information to the brain, where a certain degree of selection occurs between what is admitted and what is excluded. The brain regions concerned with nociceptive stimulus perception are the nucleus reticularis gigantocellularis (N R G C) in the reticular formation, the ventrolateral part of the hypothalamus, the intralaminar nuclei of the thalamus (and in primates also the ventrolateral nuclei of the thalamus), the amygdala and the somatosensory regions in the neocortex.

Various methods have been used to measure pain in animals; most of them are based on defensive movements and/or other motor reactions of the animal to a 'pain' stimulus. A disadvantage of such methods is that it cannot be ascertained whether the stimulus has really penetrated to the central parts of the brain or whether the movement is an unconscious reflex. There is also a danger that substances which act chiefly by blocking the efferent motor nerve system will be falsely categorized as 'pain-suppressing'.

The use of SEP makes it possible to measure the penetration of nociceptive signals into the neocortex. It is, of course, not possible to

measure the 'appreciation' of such signals in the organism, i.e. whether they are experienced as pain, but if peripherally applied noxious stimuli do not penetrate to the central regions of the brain the chance that pain is felt is nil. In human beings there is in fact a good correlation between the size of these potentials and the verbal description of the intensity of pain sensation.

Chapter 2 provides a description of the techniques of operation for implantation of electrodes in the brain and spinal cord and around the sciatic nerve. The methods of stimulation of peripheral nerves are also described; three methods were used: *electrical stimulation of the tooth-pulp* and *mechanical* and *electrical stimulation of the skin of the hind paw.*

Chapter 3 is concerned with the evoked potentials observed in dogs without anesthesia, with recordings from the sciatic nerve, spinal cord, N R G C, thalamus, hypothalamus, contralateral amygdala and the contralateral and ipsilateral somatosensory cortex I (SSC I) and II (SSC II). Both *mechanical* and *electrical* stimulation of the hind paw produced in the sciatic nerve one potential in the C fiber region, three potentials in the Aδ fiber region, one potential in the Aγ fiber region and one in the Aβ fiber region. Six potentials were also present in the spinal cord.

In the records from the brain electrodes six potentials were again observed in all cerebral regions studied, except with *electrical tooth-pulp* stimulation where the first two potentials were absent. The shift of latency times between spinal cord and brain seemed to indicate that the centrally registered potentials with a peak latency of less than 50 msec originated from Aβ and Aγ fibers, those with latencies between 50 and 150 msec from Aδ fibers and the later ones from C fibers. In particular the potentials with a latency greater than 50 msec increased greatly in amplitude with increasing intensity of the stimulus. These potentials were also practically the only ones present with *tooth-pulp* stimulation, and it is known that the tooth-pulp is richly supplied with nociceptive Aδ and C fibers. It seems probable that these potentials represent the central registration of peripherally applied nociceptive stimuli.

In Chapter 4 the effects of local and general anesthesia on these SEP are described. Lidocaine, a general anesthetic, produced a marked reduction in amplitude of the potentials with a latency time of more than 50 msec, the reduction being observed in all brain regions. Nitrous oxide reduced the amplitudes by about 50%. Halothane at higher concentrations above 2%, led to a very marked reduction of all amplitudes. Administration of 100% oxygen for 30 minutes completely restored the original values of all amplitudes.

Pentobarbital in a dosage of 15 mg/kg i.v. produced insufficient anesthesia as judged from the reduction in amplitude of the Aδ and C fiber potentials in response to stimulation; with twice this dosage the effect seemed to be sufficient. Thiopental in a dosage of 22.5 mg/kg produced sufficient anesthesia but this was of very short duration, only a few minutes.

Ketamine, 10-15 mg/kg, reduced the amplitudes to such a degree that it was evident that a good degree of anesthesia had been achieved. Fentanyl in a dosage of 0.075 mg/kg gave only a slight anesthetic effect as judged from the amplitude reduction of the SEP; higher dosage would appear desirable if sufficient anesthesia is to be attained.

Droperidol, 1 and 1.5 mg/kg, did not cause a significant reduction of the amplitudes; xylazine, 1.5 mg/kg did produce a reduction.

Decrease of amplitudes of the SEP was usually accompanied by an increase of latency times; this increase was greatest with fentanyl and, as would be expected, least with droperidol. The N R GC is the most sensitive to anesthetics, the hypothalamus and amygdala are about equal in this respect and are more sensitive thant the somatosensory cortex II; the thalamus and the SSC I are intermediate in their sensitivity to anesthetics.

Measurement of SEP seems to be a good method for testing the efficacy of analgesia and anesthesia in animals. Registration of the potentials in the somatosensory cortical regions is sufficient for this purpose, as other parts in the brain show a greater reduction of SEP under the influence of anesthetics than do these regions.

SOMATO-SENSORISCHE EVOKED POTENTIALEN IN RELATIE TOT NOCICEPTIE EN ANAESTHESIE

Deze studie is opgezet om te onderzoeken of het registreren van somato-sensorische evoked potentialen een indicatie geeft in hoeverre schadelijke, pijnlijke prikkels tot in de centrale delen van de hersenen doordringen en of de potentialen een 'graadmeter' zijn voor de mate waarin deze prikkels als 'pijn' worden gevoeld, zodat aan de afname van de amplitude en latentietijd van deze potentialen de mate van analgesie en anaesthesie kan worden 'gemeten'.

In Hoofdstuk 1 wordt de neurofysiologie van de pijn behandeld. Perifere zenuwen bestaan uit vezels van verschillende dikte, al naar gelang van de dikte van de myelineschede. Van dik naar dun worden ze verdeeld in Aα-, Aβ-, Aγ-, Aδ- en C-vezels. De A-vezels zijn myelinehoudend, de C-vezels niet. Hoe dikker de myelineschede, hoe sneller de geleiding van prikkels in de zenuwvezel is. Langzaam geleidende Aδ- en C-vezels blijken betrokken bij het doorseinen van weefselbeschadigende en dus pijnlijke prikkels. In het ruggemerg schakelen deze vezels over op opstijgende zenuwbanen, welke de informatie doorsturen naar de hersenen. Hier vindt al een zekere selectie plaats van wat wel en wat niet wordt doorgelaten. In de hersenen blijken met name de nucleus reticularis gigantocellularis in de formatio reticularis (NRGC), het ventrobasale deel van de hypothalamus, de intralaminaire nuclei van de thalamus, - en bij primaten ook de ventrolaterale nuclei van de thalamus -, de amygdala en de somato-sensorische gebieden in de neocortex bij de nociceptieve prikkelperceptie betrokken te zijn.

Verschillende methoden zijn aangewend om bij dieren pijn te meten. De meeste berusten op afweerbewegingen en/of andere motorische reacties van dieren op een 'pijn'-stimulus. Nadelen hiervan zijn dat niet kan worden bepaald of de pijnprikkel werkelijk tot in centrale delen van de hersenen doordringt of dat de beweging een niet bewuste reflex is.

Bovendien bestaat het gevaar dat stoffen welke voornamelijk het motorische, efferente zenuwstelsel blokkeren, valselijk als 'pijn onderdrukkend' worden bestempeld.

Bij het gebruik van de somato-sensorische evoked potentialen kan het tot in de neocortex doordringen van nociceptieve signalen worden gemeten. Het meten van de 'waardering' van deze prikkels in het organisme, d.w.z.

of ze als 'pijn' worden ervaren, is uiteraard niet mogelijk. Als perifeer toegediende schadelijke prikkels echter niet doorkomen in de centrale delen van de hersenen, is de kans dat er pijn gevoeld wordt afwezig. Bij mensen blijkt er overigens een goede relatie te bestaan tussen de grootte van deze potentialen en de mondelinge mededeling over de sterkte van het pijngevoel.

In hoofdstuk 2 worden de operatietechnieken beschreven van het implanteren van de electroden in de hersenen van de hond, in het ruggemerg en rondom de nervus ischiadicus. Ook de methoden van prikkeling van de perifere zenuwen worden beschreven. Drie methoden zijn hierbij gebruikt, namelijk *electrische tandpulpa stimulatie* en *mechanische* en *electrische stimulatie van de huid van de achterpoot*.

Hoofdstuk 3 handelt over de evoked potentialen welke bij honden zonder anaesthesie gevonden werden in de nervus ischiadicus, in het ruggemerg, in de NRGC, in de thalamus, in de hypothalamus, in de contralaterale amygdala en in de contralaterale en ipsilaterale somato-sensorische cortex I (SSC I) en II (SSC II).

Zowel *mechanische* als *electrische* stimulatie veroorzaakt in de nervus ischiadicus één potentiaal in het C-vezel gebied, drie potentialen in het Aδ-vezel gebied, één potentiaal in het Aγ-vezel gebied en één potentiaal in het Aβ-vezel gebied. Zes potentiaal toppen blijken ook aanwezig te zijn in het ruggemerg.

Zes potentialen blijken tevens aanwezig te zijn in alle hersengebieden. Alleen bij *electrische tandpulpa* stimulatie blijken de eerste twee afwezig te zijn. De verschuiving in latentietijden van ruggemerg naar hersenen lijkt erop te wijzen dat de centraal geregistreerde potentialen afkomstig zijn van vezels met verschil in geleidingssnelheid. De potentialen met een pieklatentie onder de 50 msec worden door Aβ- en Aγ-vezels veroorzaakt. De potentialen met een latentie tussen de 50 en 150 msec worden door Aδ-vezels en de latere door C-vezels opgewekt. Met name de potentialen met een latentietijd groter dan 50 msec nemen sterk in amplitude toe als de intensiteit van de stimulus toeneemt. Deze potentialen zijn ook vrijwel als enige aanwezig bij de *electrische tandpulpa* stimulatie. Met name de tandpulpa is rijk voorzien van nociceptieve Aδ- en C-vezels.

Het lijkt waarschijnlijk dat deze potentialen de centrale registratie zijn van perifeer toegediende nociceptieve stimuli.

In Hoofdstuk 4 tenslotte worden de effecten van lokale en algehele anaesthesie op deze somato-sensorische evoked potentialen beschreven.

Lidocaine, een lokaal anaestheticum geeft een sterke reduktie in amplitudes van de potentialen met een latentietijd boven de 50 msec. Deze reduktie was te zien in alle hersendelen. Lachgas reduceerde de amplitudes met ongeveer 50%. Halothaan in hogere concentraties boven 2% gaf een veel sterkere reduktie te zien van alle amplitudes. 100% zuurstof gedurende een half uur herstelde de grootte van de amplitudes weer volledig.

Pentobarbital in een dosis van 15 mg/kg i.v. geeft een onvoldoende anaesthesie gelet op de reduktie in amplitudes van de door Aδ- en C-vezels stimulatie opgewekte potentialen. Een dubbele dosis lijkt wel voldoende. Thiopental geeft in een dosis van 22,5 mg/kg wel een voldoende anaesthesie doch deze is van zeer korte duur, slechts enkele minuten.

Ketamine in een dosering van 10-15 mg/kg geeft een zodanige demping van de amplitudes van de evoked potentialen dat een goede anaesthesie aanwezig is.

Fentanyl in een dosis van 0,075 mg/kg geeft een lichte anaesthesie te zien, gezien de afname in amplitudes van de evoked potentialen. Een hogere dosis lijkt aanbevelenswaardig om een voldoende anaesthesie te waarborgen.

Droperidol geeft in een dosis van 1 en 1,5 mg/kg geen significante daling van de amplitudes te zien. Xylazine (1,5 mg/kg) doet de amplitudes van de evoked potentialen wel verkleinen.

Afname in de grootte van de amplitudes gaat meestal gepaard met een toename in latentietijden van de evoked potentialen. Deze toename is het sterkst bij fentanyl en het geringst bij droperidol.

De nucleus reticularis gigantocellularis is het meest gevoelig voor anaesthetica. De hypothalamus en amygdala reageren ongeveer gelijk doch zijn nog gevoeliger dan de somato-sensorische cortex II. De thalamus en de somato-sensorische cortex I ligt qua gevoeligheid voor anaesthetica daar tussenin.

Meten van SEP-en lijkt een goede methode om pijnstilling en anaesthesie te testen bij dieren. Registratie van de potentialen in de somato-sensorische cortex gebieden is hiervoor voldoende, omdat andere delen van de hersenen een sterkere demping ondervinden van anaesthesie dan deze gebieden.

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CURRICULUM VITAE

De auteur van dit proefschrift werd op 15 november 1949 te Tilburg geboren. Na de lagere school bezocht hij het St. Odulphus Lyceum te Tilburg en behaalde het einddiploma Gymnasium-β in 1969. In datzelfde jaar werd de studie in de Diergeneeskunde aangevangen aan de Rijksuniversiteit te Utrecht. In 1976 legde hij daar het dierenarts-examen af. In datzelfde jaar volgde een aanstelling als dierenarts/proefdierkundige bij het Centraal Dierenlaboratorium van de Medische Faculteit van de Katholieke Universiteit te Nijmegen

Sinds 1982 is hij werkzaam als prakticus voor kleine huisdieren te Arnhem.

STELLINGEN

BEHORENDE BIJ HET PROEFSCHRIFT VAN

A.P.M.G. BERTENS

I

Het registreren van somatosensorische evoked potentials is een betrouwbare methode om nociceptie bij dieren te meten.

II

Vooral demping van de amplitude van de somatosensorische potentialen met een latentietijd groter dan 50 msec geeft een indicatie van het analgetische vermogen van anaesthetica.

III

Het gebruik van lokaal- en geleidings-anaesthesie bij proefdieren zou meer gestimuleerd moeten worden.

IV

Het gebruik van anaesthetica tijdens metingen aan het centrale zenuwstelsel van proefdieren beïnvloedt de metingen zodanig dat de resultaten van deze experimenten met de nodige voorzichtigheid moeten worden geïnterpreteerd.

V

Proefdierkunde zou als biomedisch vakgebied ook een latijnse of griekse benaming moeten krijgen.

VI

Het gebruik van asielhonden en -katten voor chronische experimenten moet uit ethisch oogpunt ten sterkste ontraden worden.

VII

Het gezegde 'Een ezel stoot zich niet tweemaal aan eenzelfde steen' wijst erop dat ook bij dieren weefselbeschadigende stimuli met onplezierige sensaties gepaard gaan.

VIII

Pijnstilling na chirurgische ingrepen bij proefdieren verdient nadere aandacht.

IX

Het predikaat SPF, toegekend aan proefdieren met een bepaalde microbiologische status, zegt nauwelijks iets over de kwaliteit van die status. Naast de niet aanwezige ziekteverwekkers horen ook de onderzoeksmethode, monstergrootte en frequentie van onderzoek opgegeven te worden.

X

Voor het manipuleren met erfelijk materiaal is genetechnologie een betere naam dan biotechnologie.

XI

Het goed gedijen van dieren duidt vaak meer op welvaart dan welzijn van het dier.

XII

Toxicologisch onderzoek zou nieuwe homoeotherapeutische geneesmiddelen op kunnen leveren.

Nijmegen, 25 november 1983 A.P.M.G. Bertens